Uniform Medical Plan coverage limits

Updates effective 10/1/2020

The benefit coverage limits listed below apply to these UMP plans:

- Uniform Medical Plan (UMP) Classic (PEBB)
- UMP Consumer-Directed Health Plan (UMP CDHP) (PEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (PEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (PEBB)

- UMP Achieve 1 (SEBB)
- UMP Achieve 2 (SEBB)
- UMP High Deductible Plan (SEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (SEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (SEBB)

Some services listed under these benefits have coverage limits. These limits are either determined by a Health Technology Clinical Committee (HTCC) decision or a Regence BlueShield medical policy. **The table below does not include every limit or exclusion under this benefit. For more details, refer to your plan's Certificate of Coverage.**

Uniform Medical Plan Pre-authorization List

The Uniform Medical Plan (UMP) Pre-authorization List includes services and supplies that require pre-authorization or notification for UMP members.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
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Transplants and Ventricular Assist Devices

These services or supplies have coverage limits	The rules or policies that define the coverage limits	Limit applies to these codes (chosen by your provider to bill for services)
Transplants - Islet Transplantation	Regence Medical Policy Tra13	• 48160, 0584T, 0585T, 0586T, G0341, G0342, G0343
Transplants - Heart	Regence Medical Policy Tra02	• 33945
Transplants - Heart/Lung	Regence Medical Policy Tra03	• 33935
Transplants - Lung and Lobar Lung	Regence Medical Policy Tra08	• 32851, 32852, 32853, 32854, S2060
Transplants - Isolated Small Bowel Transplant	Regence Medical Policy Tra09	• 44135, 44136
Transplants - Small Bowel/Liver and Multivisceral Transplant	Regence Medical Policy Tra18	• 44135, 44136, 47135, 48554, S2053, S2054, S2152
Transplants - Liver Transplant	Regence Medical Policy Tra05	• 47135
Transplants - Pancreas Transplant	Regence Medical Policy Tra06	• 48554, S2065, S2152
Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias	Regence Medical Policy Tra45.25	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms	Regence Medical Policy Tra45.24	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150

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Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas	Regence Medical Policy Tra45.34	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia	Regence Medical Policy Tra45.36	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Acute Myeloid Leukemia	Regence Medical Policy Tra45.28	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Autoimmune Diseases	Regence Medical Policy Tra45.32	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Breast Cancer	Regence Medical Policy Tra45.29	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma	Regence Medical Policy Tra45.35	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia	Regence Medical Policy Tra45.31	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma	Regence Medical Policy Tra45.33	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer	Regence Medical Policy Tra45.26	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Hodgkin Lymphoma	Regence Medical Policy Tra45.30	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150

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Hematopoietic Cell Transplantation for Light-Chain (AL) Amyloidosis or Waldenström Macroglobulinemia	Regence Medical Policy Tra45.40	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults	Regence Medical Policy Tra45.27	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Multiple Myeloma and POEMS Syndrome	Regence Medical Policy Tra45.22	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphomas	Regence Medical Policy Tra45.23	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation for Solid Tumors of Childhood	Regence Medical Policy Tra45.37	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors	Regence Medical Policy Tra45.38	• 38205, 38206, 38232, 38240, 38241, 38242, 38243, S2140, S2142, S2150
Ventricular Assist Devices and Total Artificial Hearts	Regence Medical Policy Sur52	• 33927, 33928, 33929, 33975, 33976, 33977, 33978, 33979, L8698

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Utilization Management

These services or supplies have coverage limits	The rules or policies that define the coverage limits	Limit applies to these codes (chosen by your provider to bill for services)
Air Ambulance Transport	Regence Medical Policy UM13	• A0435, A0430, S9960 • Pre-authorization is required prior to elective fixed wing air ambulance transport. • Emergency air ambulance transports will be reviewed retrospectively for medical necessity; clinical documentation will be requested, if needed, upon receipt of the electronic claim.

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Surgery, Policy No. 52

Ventricular Assist Devices and Total Artificial Hearts

Effective: April 1, 2020

Next Review: December 2020
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Ventricular assist devices and total artificial hearts provide mechanical circulation for patients with end-stage heart disease who are waiting for, or cannot survive, a heart transplant.

MEDICAL POLICY CRITERIA

Note: This policy does not address the use of percutaneous ventricular assist devices (pVADs) which may be considered medically necessary.

I. Implantable ventricular assist devices (i.e., LVADs, RVADs and BiVADs)

A. Implantable ventricular assist devices with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** for any of the following indications (1-3):

1. As a bridge to transplantation for patients who meet all of the following criteria:

a. Currently listed as a heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation

b. Not expected to survive until a donor heart can be obtained

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2. For use in the post-cardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass.
3. As destination therapy in patients meeting all of the following criteria:
   a. End-stage heart failure
   b. Documented ineligibility for human heart transplantation
   c. One of the following criteria is met:
      i. New York Heart Association (NYHA) class III or IV* for at least 28 days who have received at least 14 days support with an intraaortic balloon pump or are dependent on intravenous inotropic agents, with two failed weaning attempts. (NYHA Class III = marked limitation of physical activity; less than ordinary activity leads to symptoms. NYHA Class IV = inability to carry on any activity without symptoms; symptoms may be present at rest.)
      ii. NYHA class IV* heart failure for at least 60 days. (NYHA Class IV = inability to carry on any activity without symptoms; symptoms may be present at rest)

B. Ventricular assist devices and aortic counterpulsation devices are considered **investigational** in all other circumstances, including but not limited to the following:
   1. Use of a non-FDA approved device.

II. Total Artificial Hearts

A. Total artificial hearts with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** as a bridge to heart transplantation in patients meeting all of the following criteria:
   1. Have biventricular failure
   2. Currently listed as heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation
   3. Not considered a candidate for a univentricular or biventricular support device
   4. Have no other reasonable medical or surgical treatment options
   5. Not expected to survive until a donor heart can be obtained

B. Total artificial hearts are considered **investigational** in all other circumstances, including but not limited to the following:
   1. Use as destination therapy
   2. Use of a total artificial heart that does not have FDA PMA, 510(k), or HDE clearance

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy

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criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- For Implantable Ventricular Assist Devices:
  - Documentation as to whether this is a bridge to heart transplant, being used post-cardiotomy for patient who is unable to be weaned of cardiopulmonary bypass, or as destination therapy
  - For destination therapy:
    - Documentation of end-stage heart failure, ineligibility for human heart transplant, and current NYHA classification, including duration of NYHA classification, symptoms, and treatments tried.
- For Total Artificial Heart:
  - Documentation that this is a bridge to heart transplant and patient has biventricular failure; is listed as heart transplant candidate or undergoing evaluation to determine candidacy for heart transplant; is not considered a candidate for univentricular or biventricular support device; has no other reasonable medical or surgical treatment options; and is not expected to survive until a donor heart can be obtained

CROSS REFERENCES

1. Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults, Medicine, Policy No. 152
2. Surgical Ventricular Restoration, Surgery, Policy No. 149
3. Heart Transplant, Transplant, Policy No. 02
4. Heart/Lung Transplant, Transplant, Policy No. 03

BACKGROUND

VENTRICULAR ASSIST DEVICES (VADS)

Biventricular, Right Ventricular, and Left Ventricular Devices

There are three kinds of ventricular assist devices: biventricular (BiVADs), right ventricular (RVADs), and left ventricular (LVADs). Surgically implanted ventricular assist devices (VADs) are attached to the native heart and vessels to provide temporary mechanical circulatory support by augmenting cardiac output. LVADs to support the left ventricle are the most commonly used VADs, but right ventricular and biventricular devices may also be used. LVADs are most commonly used as a bridge to transplantation for those patients who are not expected to survive without mechanical support until a heart becomes available. LVADs may also be used as a bridge to recovery in patients with reversible conditions affecting cardiac output (e.g., post-cardiotomy cardiogenic shock). More recently, given the success of LVADs for prolonged periods of time, there has been interest in using LVADs as permanent "destination" therapy for patients with end-stage heart disease who are not candidates for human heart transplantation due to age or other comorbidities.

Aortic Counterpulsation Devices

Intra-aortic balloon pump (IABP) devices have been developed as a treatment for cardiogenic shock. IABPs consist of a helium-filled balloon placed in the aorta that deflates during cardiac systole to increase forward blood flow. The inflation and deflation of the balloon is computer-

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controlled and can be regulated by either a pressure-sensing catheter or an electrocardiogram. These devices have not been FDA approved.

TOTAL ARTIFICIAL HEARTS

The total artificial heart (TAHs) replaces the native ventricles and is attached to the pulmonary artery and aorta; the native heart is typically removed. TAHs may be implanted temporarily as a bridge to heart transplantation or permanently as destination therapy in those who are not candidates for transplantation.

The CardioWest™ Total Artificial Heart is a temporary TAH, which is used in the inpatient hospital setting as a bridge to heart transplantation. The CardioWest TAH is implanted after the native ventricles have been excised. The AbioCor® Implantable Replacement Heart is a permanent TAH currently available as destination therapy for people who are not eligible for a heart transplant and who are unlikely to live more than a month without intervention. The device has an internal battery that allows the recipient to be free from all external connections for up to one hour. The system also includes two external batteries that allow free movement for up to two hours. During sleep and while batteries are being recharged, the system can be plugged into an electrical outlet. In order to receive the AbioCor® artificial heart, in addition to meeting other criteria, patients must undergo a screening process to determine if their chest volume is large enough to hold the two-pound device which is too large for about 90% of women and many men.

REGULATORY STATUS

Device Name	Device Type	Manufacturer	FDA Approval	Indication
HeartMate II®	LVAD	Thoratec Corp.	PMA	Bridge to transplant and destination therapy
HeartMate 3™	LVAD	Thoratec Corp.	PMA	Bridge to transplant and destination therapy
Thoratec® IVAD	BiVAD	Thoratec Corp.	PMA + Supplement	Bridge to transplant and post-cardiotomy
Levitronix Centrimag®	RVAD	Levitronix, LLC	HDE	Postcardiotomy (temporary circulatory support for up to 14 days)
Novacor®	LVAD	World Heart, Inc.	PMA	Bridge to transplant
DeBakey VAD® Child	LVAD	MicroMed Technology, Inc.	HDE	Bridge to transplant in children 5-16 years of age
EXCOR® Pediatric System	BiVAD	Berlin Heart, Inc.	HDE	Bridge to transplant, pediatric (newborns to teens)
Jarvik 2000	LVAD	Jarvik Heart, Inc.	*IDE-Investigational*†	
HeartWare® Ventricular Assist System (HVAD®)	VAD	Heartware Intl., Inc.	PMA	Bridge to transplant – for use in-hospital or out-of-hospital

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Device Name	Device Type	Manufacturer	FDA Approval	Indication
AutoCat 2 WAVE® IABP System	IABP	Arrow Intl., Inc.	none	
Maquet CS300™ IABP	IABP	Maquet Cardiovascular, LLC	none	
SynCardia Temporary TAH (formerly called CardioWest™)	Temporary total artificial heart	SynCardia Systems, Inc.	510(k)	Bridge to transplant – for use inside the hospital
AbioCor® TAH	Implantable Replacement Heart System	AbioMed, Inc.	HDE	Destination therapy

†FDA Investigational Device Exemption (IDE) is not considered a full FDA approval. Devices with an IDE designation are considered investigational.

In August 2015, the U.S. Food and Drug Administration (FDA) published a safety communication about serious adverse events with implantable left ventricular assist devices.[1]

In August 2016, HeartWare® recalled its VAD Pumps due to a design flaw that was deemed by FDA as potentially causing serious injuries or death (class I recall). The devices affected were manufactured and distributed from March 2006 and May 2018. FDA product codes: 204 and 017.

A class I recall was issued for the HeartMate 3™ in April 2018 affecting all manufacturing dates. FDA product code: DSQ.

Although adverse events have been reported, the FDA recognizes “that LVADs are life-sustaining, life-saving devices for patients with advanced left ventricular heart failure. When used for the currently approved indications in appropriately selected patients, we believe the benefits of these LVADs continue to outweigh the risks”

EVIDENCE SUMMARY

The principal outcome associated with treatment of refractory heart failure (HF) is to prolong survival, either temporarily as a bridge to decision, recovery, or heart transplantation, or permanently as a replacement for the damaged heart in patients who are not candidates for heart transplantation.

VENTRICULAR ASSIST DEVICES

BRIDGE TO TRANSPLANTATION, LEFT VENTRICULAR ASSIST DEVICES

Systematic Reviews

A systematic review published in 2011 supported the conclusions reached in the 1996 BCBSA TEC assessment.[2,3] The 2011 review included 31 observational studies that compared outcomes of transplant in patients who did and did not have pre-transplant left ventricular assist devices (LVADs). Survival at one year was more likely in patients who had

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LVAD treatment, but this benefit was confined to patients who received an intra-corporeal device (relative risk [RR]: 1.8, 95% confidence interval [CI] 1.53 to 2.13). For patients treated with an extracorporeal device, the likelihood of survival was not different from patients who were not treated with an LVAD (RR: 1.08, 95% CI 0.95 to 1.22). There was no difference in the risk of rejection between patients who did and did not receive LVAD treatment.

Nonrandomized Studies

Adult patients

Additional reports not included in the 1996 TEC assessment or the 2011 systematic review are consistent with the above analysis.[4-6] It should be recognized that left ventricular assist devices cannot change the number of patients undergoing heart transplantation due to the fixed number of donor hearts. However, the LVAD will categorize its recipient as a high priority heart transplant candidate. Currently available LVADs consist of pulsatile devices that require both stiff power vent lines that perforate the skin and bulky implantable pump chambers. There is considerable research interest in developing non-pulsatile axial flow systems that have the potential for small size and low-noise levels.[7-12]

Aissaoui (2018) published an observational study comparing 224 patients in Germany and France with end-stage heart failure who received VAD as first option (group I, n=83) or either heart transplantation or medical therapy as first option (group II, n=141).[13] The estimated two-year survival was 44% for group I and 70% for group II (p<0.001). The study was limited by the lack of randomization and possible patient selection bias.

Grimm (2016) compared outcomes for patients based on the duration of LVAD use, using data from the United Network for Organ Sharing database.[14] Of the 1,332 included patients, 130 (9.8%) were classified as short duration (< 90 days), 729 (54.7%) were classified as intermediate duration (90 to 365 days), and 473 (35.5%) were classified as long duration (>365 days). A greater proportion of patients in the intermediate and long duration groups were considered functionally independent prior to transplantation compared with the short duration patients. There was no difference in 30-day survival, six-month survival, or one-year survival between the groups. Also, despite worse renal function in the intermediate and long-term groups, there was no difference between groups in new-onset post-transplant renal failure.

Another report by Grimm (2016),which used the United Network for Organ Sharing database, suggested that patients bridged to transplant with an LVAD have better outcomes than those bridged with TAH or biventricular assist devices.[15] Cheng (2016) compared BiVAD to TAH outcomes in this database, and found similar wait-list survival between the groups.[16]

Deo (2014) reported no significant differences in outcomes for 37 patients bridged to transplant with a ventricular assisted device (VAD) and 70 patients who underwent a heart transplant directly.[17] In 2013, Slaughter reported combined outcomes for patients included in the HeartWare® bridge-to-transplant study.[18] The study included 322 patients with heart failure, eligible for heart transplant, who received the HeartWare® (140 patients from the original study; 190 patients in the continue-access protocol) who were monitored to outcome or had completed 180 days of follow-up at the time of this analysis. Survival at 60, 180, and 360 days was 97%, 91%, and 84%, respectively. The most common adverse events were respiratory dysfunction, arrhythmias, sepsis, and driveline exit-site infections. Patients generally had improvements in quality of life measures.

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Aaronson (2012) reported results of a multicenter, prospective study of a newer generation LVAD, the HeartWare®, which is a smaller, continuous flow centrifugal device that is implanted in the pericardial space.[19] The study enrolled 140 patients who were awaiting heart transplantation who underwent HeartWare® implantation. A control group of 499 subjects was comprised of patients drawn from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, which collects data on patients who receive FDA-approved durable mechanical circulatory support devices. The study's primary outcome was defined as survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days. Secondary outcomes were comparisons of survival between groups and functional, quality of life, and adverse event outcomes in the HeartWare® group. Success occurred in 90.7% of the HeartWare® group and 90.1% of controls ($p<0.001$, noninferiority with a 15% margin). Serious adverse events in the HeartWare® group included, most commonly, bleeding, infections, and perioperative right heart failure.

Evidence suggests that the HeartMate II® axial achieves similar or better results than the earlier pulsatile HeartMate I model. In six reports with samples ranging from 32 to 279 patients, most participants received the new device as a bridge to transplantation.[20-25] Survival rates at six months and one year were 67% to 87%, and 50% to 80%, respectively. These rates are similar to those reported from INTERMACS.[26] An additional report from INTERMACS comparing the HeartMate II® to other LVAD devices for patients who received them with a bridge to transplantation indication reported that 80% and 91% of HeartMate II® and other LVAD patients reached transplant, cardiac recovery, or ongoing LVAD support by six months.[27] One report, however, compared HeartMate I and HeartMate II® recipients at a single center, finding the same one year survival and similar rates of subsequent development of right heart failure.[22] Serious adverse events occurring after HeartMate II® implantation included bleeding episodes requiring reoperation, stroke, infection, and device failure. A European study that included 67 bridge to transplant patients and 31 destination therapy patients found similar one-year survival rates in the two groups: 63% and 69%, respectively. A report on HeartMate II® recipients at a single institution found that out of 250 LVAD patients between November 2011 and June 2016, 6% (16) required a device pump exchange during the study period, and all but one patient survived until hospital discharge.[28]

Pediatric Patients

Publications on children using VADs as a bridge to transplantation have reported positive outcomes. For example, a retrospective study of all children listed for a heart transplant at a single center between 1993 and 2009 found that mortality dropped significantly after the availability of VADs.[29] Davies (2008) reported that pediatric patients requiring a pretransplantation VAD had similar long-term survival to those not receiving mechanical circulatory support.[30]

A retrospective registry study by Jeewa (2018) assessed long-term outcomes for pediatric VAD use as a bridge to transplantation in patients from the Berlin Heart investigational device exemption trial.[31] These patients (n=109) were compared with matched controls from the Pediatric Heart Transplant Study who did not require mechanical circulatory support (n=166). There was no significant difference between the groups for five-year survival (81% for VAD, 88% for non-VAD, $p=0.09$) or for rates of infection or rejection.

Bulic (2017) identified all U.S. children between 1 and 21 years of age at heart transplant between 2006 and 2015 for dilated cardiomyopathy who were supported with an LVAD or

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vasoactive infusions alone at the time of heart transplant from the Organ Procurement and Transplant Network registry (n=701).[32] Children receiving LVAD were older, on a higher level of hemodynamic support, more likely to be on dialysis and waited long to receive a donor heart than children receiving vasoactive infusions. Functional status as measured by the median Karnofsky Performance Scale at heart transplant was higher for children receiving LVAD compared with vasoactive infusion (6 vs 5, p<0.001) and children receiving LVAD were more likely to be discharged from the hospital at the time of transplant. The percent of children having stroke at the time of transplant was higher in those receiving LVAD (3% vs 1%, p=0.04).

Almond (2013) reported results from a prospective, multicenter registry to evaluate outcomes in children who received the Berlin Heart EXCOR® device as a bridge to transplant.[33] All patients were followed up from the time of EXCOR® implantation until transplantation, death, or recovery. The study included 204 children, 67% of whom received the device under compassionate use. Survival at 12 months on EXCOR® support was 75%, including 64% who survived to transplantation, 6% who recovered (device explanted and patient survived 30 days), and 5% alive with the device in place. In a follow-up study which evaluated 204 children from the same registry, Jordan reported relatively high rates of neurologic events in pediatric patients treated with the EXCOR® device (29% of patients), typically early in the course of device use.[34] A 2016 report on this group included 358 bridge-to-transplant EXCOR® patients, and found that short- and mid-term post-transplant survival in these patients was similar to that of patients who did not receive pre-transplant mechanical circulatory support.[35]

Wehman (2016) reported on post-transplant survival outcomes for pediatric patients who received a VAD, extracorporeal membrane oxygenation (ECMO), or no mechanical circulatory support, in the pre-transplant period.[36] The study included 2,777 pediatric patients who underwent heart transplant from 2005 to 2012, who were identified through the United Network for Organ Sharing Database, of whom 428 were bridged with VADs and 189 were bridged with ECMO. In unadjusted analysis, the actuarial five-year survival was highest in the direct-to-transplant group (77%), followed by the VAD group (49%) and then the ECMO group (35%). In a proportional hazards model to predict time to death, restricted to the first four months post-transplant, ECMO bridging was significantly associated with higher risk of death (adjusted hazard ratio [HR] 2.77 vs direct-to-transplant, 95% CI 2.12 to 3.61, p<0.0001). However, a model to predict time to death excluding deaths in the first four months post-transplant, the bridging group was not significantly associated with risk of death.

Section Summary

In adults, the evidence on the efficacy of LVADs as bridge to transplant consists of numerous nonrandomized studies comparing different LVADs devices among patients who have no other treatment options. In children, the evidence consists of several nonrandomized studies. These studies report that substantial numbers of patients survive the transplant in situations in which survival would not be otherwise expected. Despite the lack of high-quality studies, this evidence is sufficient to determine that outcomes are improved in patients who have no other options for survival.

VENTRICULAR ASSIST DEVICES AS BRIDGE TO RECOVERY

VADs may have a role in bridging patients to recovery, particularly if there is reverse remodeling of the left ventricle. Several additional studies have investigated the role of VADs in bridging patients to decision.

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Nonrandomized Studies

Support from VADs was originally indicated for the treatment of postcardiotomy cardiogenic shock in patients who could not be weaned from cardiopulmonary bypass. VAD use in this setting is temporary and brief, lasting between 1.4 and 5.7 days. The overall salvage rate for this indication is low, at approximately 25%; however, without VAD support, patients with refractory postcardiotomy cardiogenic shock would experience 100% mortality.[6,37,38]

Agrawal (2018) published a retrospective cohort study evaluating the 30-day readmissions of 2,510 patients undergoing LVAD implantation.[39] Of the patients who met the inclusion criteria, 788 (31%) were readmitted within 30 days after surviving initial index hospitalization. Cardiac causes accounted for 23.8% of readmissions, 13.4% due to heart failure, and 8.1% to arrhythmias. Infection (30.2%), bleeding (17.6%), and device-related causes (8.2%) comprised the 76.2% of non-cardiovascular causes for readmission. The study's limitations relate to the nature of nonclinical data collection and gaps in current subject knowledge.

A retrospective cohort study by Adesyiun (2017) assessed LVAD complications and overall effect on mortality to determine factors associated with development of early and long-term complications.[40] Utilizing logistic regression and Cox proportional hazards analyses at univariable and multivariable stages, the study found 24% of patients developed early complications and 18.5% developed both early and late complications. There was a significant association between death and early complications (p=0.017), while the additional presence of two or more complications produced a 2.7-fold increase in mortality odds (p=0.016). Mortality odds increased by 20% with each subsequent complication (p=0.004). The study was limited in that, during its long, 13-year team span, practice associated with LVAD maintained had changed but were not address by the study. Further limitations include the difficulty in determining the strictness to which a patient might have met the complication definitions, as well as the small sample size of the study.

Kawajiri (2017) evaluated the outcomes of patients with end-stage heart failure who had conventional surgery as opposed to transplant or mechanical support.[41] A total of 133 patients of this retrospective cohort study were identified with left ventricular ejection fraction (LVEF) less than 20% and VO2 max < 14 mL/min/m^2 and, after initial referral for advanced therapies, were instead offered a conventional procedure. Of the originally identified 133 patients, 68 were determined transplant eligible. Actuarial survival at 5 and 10 years was 72% and 39%, respectively, after 12% in-hospital mortality. Outcomes were acceptable for conventional cardiac surgery in highly selected patients with end-stage HF, and long-term survival was comparable with advanced surgical therapies. The study was limited by a small study population, its nonclinical nature, and the potential underestimation the VAD/transplant mortality by measuring survival dates starting from first surgery as opposed to date of decision.

Raju (2017) focused their retrospective cohort study on consecutive LVAD patients who received more than one year of total LVAD support time.[42] During the study period, 103 patients received LVADs, 37 received LVAD support for more than one year, and 18 received support for more than two years. Average support time was 786 days. Mortality and hospital readmissions were used to determine the efficacy of continuous-flow LVADs. During a median follow-up of two years, the one-year conditional survival was 74%. Readmission reasons were due to major infection (24%), major bleeding (19%), and device malfunction/thrombosis (13%), and totaled 112 completed readmission procedures, 60% of which were done in 13% (n=5) of patients. The study had the limitations of a descriptive retrospective analysis and small sample

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size, and quality of life (QOL) self-assessments would have provided necessary patient perspective.

Takayama (2014) reported outcomes for a retrospectively-defined cohort of 143 patients who received a CentriMag® VAD as a “bridge to decision” for refractory cardiogenic shock due to a variety of causes.[43] Patients were managed with a bridge-to-decision algorithm. Causes of cardiogenic shock included failure of medical management (n=71), postcardiotomy shock (n=37), graft failure post-heart transplantation (n=2), and right ventricular failure post-implantable LVAD (n=13). The device configuration was biventricular in 67%, isolated right VAD in 26%, and isolated left VAD in 8%. After a mean duration of support of 14 days (interquartile range 8 to 26 days), 30% of patients had myocardial recovery, 15% had device exchange to an implantable VAD, and 18% had a heart transplantation.

Acharya (2016) reported on patients who underwent VAD placement in the setting of acute myocardial infarction (AMI) who were enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, a prospective national registry of FDA-approved durable mechanical circulatory support devices.[44] Patients who had an AMI as the admitting diagnosis or a major myocardial infarction (MI) as a hospital complication that resulted in VAD implantation (n=502) were compared with patients who underwent VAD implantation for non-AMI indications (n=9,727). Patients in the AMI group were generally sicker at baseline, with higher rates of smoking, severe diabetes, and peripheral vascular disease, but had fewer cardiac surgeries and recent cardiovascular hospitalizations. Most AMI patients (53.8%) were implanted with a “bridge-to-candidacy” strategy. At one-month post VAD, 91.8% of the AMI group were alive with the device in place. At one-year post-VAD, 52% of the AMI group were alive with the device in place, 25.7% had received a transplant, 1.6% had their VAD explanted for recovery, and 20.7% died with the device in place. Another retrospective study of 15,138 patients in the INTERMACS registry found that the incidence of recovery was significantly higher in bridge-to-recovery patients than in non-bridge-to-recovery patients (11.2% vs 1.2%, $p<0.0001$).[45]

Topkara (2016) reported a similar analysis of 13,454 INTERMACS adults with implants between June 2006 and June 2015 without TAH, pulsatile-flow LVAD, or heart transplant.[46] Device explant rates for cardiac recovery were 0.9% at one-year, 1.9% at two-year, and 3.1% at three-year follow-up. An additional 9% of patients demonstrated partial cardiac recovery.

In a smaller single-center retrospective cohort study, Mohamedali (2015) reported outcomes for 48 patients treated with biventricular support with the CentriMag® device as a “bridge to decision”, 18 of whom had biventricular support with venoarterial (VA) extracorporeal membrane oxygenation (ECMO), while the remainder received just biventricular VAD support.[47] Overall, 23 patients were explanted, nine to recovery, 14 to a durable LVAD, with three additional patients explanted for withdrawal of care. However, given that the study included patients who received VA ECMO, it is difficult to assess the relative impact of VAD support alone.

Six studies using the Centrimag® RVAD included between 12 and 32 patients, the majority of whom received biventricular devices.[38,48-52] Indications and numbers of patients in these five studies were: support for post-cardiotomy cardiogenic shock (bridge to recovery), bridge to long-term device implantation (n=9), treatment of right heart failure in patients who previously received LVADs, bridge to later decision when neurologic status is clarified, and acute donor graft failure. The mean time on mechanical circulatory support ranged from 9.4 days to 46.9

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days. The 30-day mortality rates were between 17% and 63%. The proportion of patients discharged from the hospital was between 30% and 83%. Major complications included bleeding requiring reoperation, sepsis, and stroke. No device failures were observed in these studies.

In a prospective multicenter study to assess myocardial recovery in patients with LVAD implantation as a bridge to transplant, Maybaum (2007) evaluated 67 patients with heart failure who had undergone LVAD implantation for severe heart failure.[53] After 30 days, patients demonstrated significant improvements compared with pre-LVAD state in LVEF (17.1% vs 34.12%, $p<0.001$), left ventricular end-diastolic diameter (7.1 cm vs 5.1 cm, $p<0.001$), and left ventricular mass (320 g vs 194 g, $p<0.001$). However, only 9% of patients demonstrated enough recovery to have their LVAD explanted.

In a 2006 study, a series of 15 patients with severe heart failure due to nonischemic cardiomyopathy underwent implantation of LVADs, along with medical management designed to enhance myocardial recovery.[54] Eleven of 15 patients had enough myocardial recovery to undergo LVAD explantation; two patients died after explantation. Among those who survived, the cumulate rate of freedom from recurring heart failure was 100% and 88.9%, respectively, at one- and four-years post explantation. The same group subsequently reported results of their LVAD explantation protocol among patients with severe heart failure due to nonischemic cardiopathy who had nonpulsatile LVADs implanted.[55] They included 20 patients who received a combination of angiotensin converting enzyme ACE inhibitors, beta blockers, and adosterol antagonists followed by the β2-agonist clenbuterol. One patient was lost to follow-up and died after 240 days of support. Of the remaining 19 patients, 12 (63.2%) were successfully explanted after a mean 286 days; estimated survival without heart failure recurrence was 83.3% at one and three years.

Section Summary

The studies previously outlined indicate that a subset of patients who receive a VAD as a bridge to transplant demonstrate improvements in their cardiac function, sometimes to the point that they no longer require the VAD. However, questions remain about defining and identifying the population most likely to experience cardiac recovery with VAD placement. One clearly defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting. Finally, current evidence is insufficient to allow the identification of other heart failure patient populations who might benefit from the use of a VAD as a specific bridge-to-recovery treatment strategy. Ongoing research studies are addressing this question, along with protocols for transitioning patients off VAD use.

LEFT VENTRICULAR ASSIST DEVICES AS DESTINATION THERAPY

Technology Assessment

The policy statement regarding LVADs as destination therapy was initially based on a 2002 TEC assessment[56] that offered the following observations and conclusions:

- The available evidence comes from a single, well-designed and rigorously conducted randomized trial, known as the REMATCH study.[57] The study was a cooperative effort of Thoratec, Columbia University and the National Institutes of Health.

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- The randomized trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation have significantly better survival on an LVAD compared with treatment by optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse events were more common in the LVAD group, but these appear to be outweighed by this group's better outcomes on function. NYHA Class was significantly improved, as was quality of life among those living to 12 months.
- LVAD patients spend a greater relative proportion of time inside the hospital than medical management patients do, but the survival advantage would mean a longer absolute time outside the hospital.

Randomized Controlled Trials

Park published a further follow-up of patients in the REMATCH trial, mentioned in the above TEC assessment, which found that survival and quality of life benefits were still apparent with extended two-year follow-up.[58]

Nonrandomized Studies

Jorde (2014) published results from an FDA-required postapproval study of the HeartMate II® device for destination therapy.[59] The study included the first 247 HeartMate II® patients identified as eligible for the device as destination therapy, outcomes and adverse events did not differ significantly from those treated in the original trial, which compared patients who received the HeartMate II® to earlier generation devices (Slaughter [2009], described below).[60] Survival in the postapproval cohort was 82% and 69% at one and two years postoperatively, respectively.

A subsequent prospective observational study comparing LVAD support (n=97) with optimal medical therapy (n=103) for patients with heart failure not requiring inotropes also reported superior survival and health-related quality of life in LVAD-treated patients.[61] Twelve-month survival was 80% in the LVAD group, compared with 63% in the best medical therapy group (p=0.022).

In addition, other case series suggest continuing improvement in outcomes related to ongoing improvements in the device and in patient management.[62] However, the durability of the HeartMate device used in the REMATCH trial is a concern; for example, at one participating institution, all six long-term survivors required device change-outs. Next generation devices consisting of smaller continuous flow devices are eagerly anticipated.

Section Summary

The primary evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is from the REMATCH study. This study reported that the use of LVADs led to improvements in survival, quality of life, and functional status.

DEVICE COMPARISONS

The mechanism of operation of LVADs has changed since their introduction. The earliest devices were pulsatile positive displacement pumps. The pulsatile pumps have been largely replaced by axial continuous-flow pumps. More recently centrifugal continuous-flow pumps have also been introduced.

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The evidence of the comparative efficacy of centrifugal continuous-flow vs axial continuous-flow devices consists of two RCTs of two different centrifugal continuous-flow devices.[63-65] The MOMENTUM3 trial compared HeartMate 3™ centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as a bridge to transplant or destination therapy. HeartMate 3™ received PMA approval in August 2017 but was recalled in April 2018. The ENDURANCE trial compared HeartWare® centrifugal continuous-flow device with the HeartMate II® axial continuous-flow device in patients indicated for circulatory support as destination therapy. HeartWare® is FDA-approved for bridge to transplantation. Both trials found the centrifugal device to be noninferior to the axial device for the primary, composite outcome including measures of survival, freedom from disabling stroke, and freedom from device failure. While there are fewer device failures with the centrifugal devices without significant increase in disabling stroke, the HeartWare® device was associated with increased risk of any stroke over a period of two years.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of an RCT and several nonrandomized comparative studies. The RCT reported fairly large differences in a composite outcome measure favoring the continuous-flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes.[60] Other nonrandomized comparative studies, including a database study with large numbers of patients, have not reported important differences in clinical outcomes between devices.

Slaughter (2009) published data from an unblinded randomized multicenter trial.[60] Subjects were randomized to continuous-flow or pulsatile-flow devices on a 2:1 block-randomization basis. The primary outcome measured was a composite endpoint of two-year survival, free of disabling stroke or need for device replacement. Continuous-flow patients (n=134) reached the primary outcome at a rate of 46% (95% CI 38 to 55) compared to pulsatile-flow patients (n=66) rate of 11% (95% CI 3 to 18), which was a significant difference ($p<0.001$). Analysis of constituent factors indicated that a lower rate of devices needing replacement in the continuous-flow group had the largest effect on the composite endpoint; two-year death rate also favored this device (58% vs. 24%, $p=0.008$). Stroke and death (within two years of implantation) were similar in the two groups (stroke rate 12% and death rate 36%). Quality of life scores were also similar in the two groups. Although unblinded, this randomized trial adds to the evidence favoring continuous-flow devices.

Nonrandomized Studies

Dell'Aquila (2014) compared outcomes for patients treated with a third-generation continuous flow device, the HeartWare® device, with those for patients treated with earlier generation devices in a single-center study.[66] Comparison-group patients received either an earlier generation continuous flow device or a pulsatile flow device. Of 287 patients who received VAD support from 1993 to 2012, 52 received a HeartWare® device, 76 an earlier generation continuous flow device, and 159 a pulsatile device. Survival was significantly better for patients who received a third-generation device, with 24 months survival of 70.4%, compared with 33.7% for patients who received an earlier generation continuous flow device and 33.8% for patients who received a pulsatile flow device ($p=0.013$). The difference in survival associated with third generation devices was more pronounced for higher scores on the INTERMACs scale.

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Nativi (2011) published a nonrandomized comparison of pulsatile versus continuous flow devices using data from the registry of the International Society for Heart and Lung Transplantation on 8,557 patients undergoing transplant.[67] Comparisons were made among patients receiving a pulsatile LVAD, a continuous flow LVAD, and no LVAD. Two time periods were used for analysis, the first was pre-2004, when nearly all LVADs were pulsatile devices, and post-2004 when continuous use devices began to be used in clinical care. There was a significantly greater risk of mortality in the first time period compared to the second time period (RR 1.30, 95% CI 1.03 to 1.65, p=0.03). When analysis was confined to the second time period, there was no significant improvement in survival for the continuous group compared to the pulsatile group (RR 1.25, 95% CI 1.03 to 1.65, p=0.03).

Other nonrandomized studies that have compared outcomes from different types of LVADs have been smaller and/or focused on physiologic outcomes.[68-71] In some of these studies, the continuous flow devices exhibit greater improvement in physiologic measures, but none of these studies have reported significant differences between devices in clinical outcomes.

Section Summary

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AORTIC COUNTERPULSATION DEVICES

Intra-aortic balloon pump (IABP) devices have been developed as a treatment for cardiogenic shock. IABPs consist of a helium-filled balloon placed in the aorta that deflates during cardiac systole to increase forward blood flow. The inflation and deflation of the balloon is computer-controlled and can be regulated by either a pressure-sensing catheter or an electrocardiogram. These devices have not been FDA approved, and therefore the evidence for these devices is not reviewed in detail.

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BRIDGE TO TRANSPLANTATION

Nonrandomized Studies

In 2004, the CardioWest Total Artificial Heart (now called the SynCardia Total Artificial Heart) received FDA approval for use as a bridge to transplant. The approval was based on the results of a nonrandomized, prospective study of 81 patients.[72] Patients had failed inotropic therapy and had biventricular failure and thus were not considered appropriate candidates for an LVAD. The rate of survival to transplant was 79%, which was considered comparable to the experience with LVAD in patients with left ventricular failure. The mean time from entry into the study until transplantation or death was 79.1 days.

Other case series have been reported on outcomes of the TAH as a bridge to transplant. For example, Copeland reported on 101 patients treated with the SynCardia artificial heart as a bridge to transplant.[73] All patients either met established criteria for mechanically assisted circulatory support or were failing medical therapy on multiple inotropic drugs. The mean support time was 87 days, with a range of 1 to 441 days. Survival to transplant was 68.3% (69/101). Of the 32 deaths prior to transplant, 13 were due to multiple organ failure, 6 were due to pulmonary failure, and four were due to neurologic injury. Survival after transplant at 1, 5, and 10 years, respectively, was 76.8%, 60.5%, and 41.2%.

DESTINATION THERAPY

In currently available studies, the AbioCor® Implantable Replacement Heart has only been used as destination therapy for end-stage patients with congestive heart failure.

Nonrandomized Studies

Torregrossa (2014) reported on 47 patients who received a TAH at 10 worldwide centers and had the device implanted for more than one year.[74] Patients were implanted for dilated cardiomyopathy (n=23), ischemic cardiomyopathy (n=15), and “other” reasons (n=9). Over a median support time of 554 days (range, 365-1373 days), 34 patients (72%) were successfully transplanted, 12 patients (24%) died while on device support, and one patient (2%) was still supported. Device failure occurred in five patients (10%). Major complications were common, including systemic infection in 25 patients (53%), driveline infections in 13 patients (27%), thromboembolic events in nine patients (19%) and hemorrhagic events in seven patients (14%). Two of the deaths occurred secondary to device failure

Dowling (2004) reported on the first seven patients in the AbioCor® clinical trial.[75] The 30-day survival rate was 71% compared with the predicted survival rate of 13% with only medical therapy. At 60 days, 43% were still alive and as of July 2006 two patients were still alive 234 and 181 days postoperatively and remain hospitalized. Deaths were due to intraoperative bleeding at the time of implantation, cerebrovascular accidents, pulmonary embolism, and multiorgan failure. No reports of serious device malfunction have been reported for the seven patients. Frazier (2004) reported information on four additional patients receiving the AbioCor®.[76] Using the same inclusion criteria as in the above RCT the device supported three patients for greater than 100 days, whereas a fourth patient expired at 53 days. There were no device related problems reported.

SECTION SUMMARY

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There is little evidence on the use of TAH as a bridge to transplantation, or as destination therapy, compared with the use of LVADs. The type of evidence on bridge to transplant is similar to that for LVADs (i.e., case series reporting substantial survival rates in patients without other alternatives). Therefore, this evidence is sufficient to conclude that TAH improves outcomes for these patients similar to LVADs and is a reasonable alternative for patients who require bridge to transplantation but who are ineligible for other types of support devices. Although TAHs show promise for use as destination therapy in patients who have no other treatment options, the available data on their use is extremely limited. There is insufficient evidence on the use of TAH as destination therapy to support conclusions about the efficacy of TAH in this setting.

PRACTICE GUIDELINE SUMMARY

SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

In 2015, the Society for Cardiovascular Angiography and Interventions (SCAI), the Heart Failure Society of America (HFSA), the Society of Thoracic Surgeons (STS), the American Heart Association (AHA), and the American College of Cardiology (ACC) published a clinical expert consensus statement on the use of percutaneous mechanical circulatory support (MCS) devices in cardiovascular care.[77] This statement addressed intra-aortic balloon pumps (IABPs), left atrial (LA)-to-aorta assist device (eg, TandemHeart), left ventricle (LV)-to-aorta assist devices (eg, Impella), extracorporeal membrane oxygenation (ECMO), and methods of right-sided support. Specific recommendations are not made, but the statement reviews the use of MCS in patients undergoing high-risk percutaneous intervention (PCI), those with cardiogenic shock, and those with acute decompensated heart failure.

AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION / AMERICAN HEART ASSOCIATION / HEART FAILURE SOCIETY OF AMERICA (ACCF/AHA/HFSA)[78]

The 2013 ACCF/AHA practice guidelines for the management of heart failure included the recommendations below related to MCS which includes LVADs. All of these recommendations were rated II.a., level of evidence B, defined as a recommendation in favor of the treatment being useful, with some conflicting evidence from a single RCT or nonrandomized studies.

- MCS is considered beneficial in carefully selected patients with stage D heart failure with reduced ejection fraction (HFrEF) as a bridge to transplantation or recovery.
- Nondurable mechanical cardiac support including percutaneous and extracorporeal VADs are considered “reasonable” as a bridge to recovery or a bridge to decision for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.
- Durable (permanent) MCS is considered reasonable to prolong survival for carefully selected patients with stage D HFrEF.

The guidelines note that, although optimal patient selection for MCS is an area of investigation, general indications for referral for MCS therapy include patient with LVEF<25% and NYHA class III-IV functional status despite guideline-directed medical therapy (GDMT) including cardiac resynchronization therapy (CRT), when indicated, with either high predicted one- to two-year mortality or dependence on continuous parenteral inotropic support.

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In 2017, the ACCF/AHA/HFSA published a focused update of the 2013 recommendations released by the ACCF and AHA.[79] LVAD was one of several treatment options recommended for patients with refractory NYHA class III or IV heart failure (stage D). If symptoms were not improved after guideline-directed management and therapy, which included pharmacologic therapy, surgical management and/or other devices, then LVAD was presented as an additional treatment option. The 2017 update focused on changes in sections regarding biomarkers, comorbidities, and prevention of heart failure, while many of the previous recommendations remained unchanged.

THE HEART FAILURE SOCIETY OF AMERICA (HFSA)

The HFSA published guidelines in 2010 on surgical approaches to the treatment of heart failure. The guidelines are based on evidence and expert opinion.[72] The following recommendations were made regarding ventricular assist devices:

- Bridge to transplantation: Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for a mechanical support device as a bridge to transplant. (Strength of Evidence B - cohort and case-control studies)
- Bridge to recovery: Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a "bridge to decision." These patients should be referred to a center with expertise in the management of patients with advanced HF. (Strength of Evidence C - expert opinion)
- Destination Therapy: Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center. (Strength of Evidence B - cohort and case-control studies)

SUMMARY

VENTRICULAR ASSIST DEVICES

There is enough research to show that implantable ventricular assist devices (VADs) as a bridge to transplantation or recovery, or as destination therapy, improve health outcomes in some patients with heart failure who might not otherwise survive. Therefore, implantable VADs may be considered medically necessary when the policy criteria are met.

There is not enough research to show that ventricular assist devices or aortic counterpulsation devices improve health outcomes for people with heart failure or other heart conditions when policy criteria are not met. Therefore, the use of ventricular assist devices or aortic counterpulsation devices when policy criteria are not met is considered investigational.

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There is enough research to show that the use of a total artificial heart (TAH) as a bridge to heart transplantation improves survival and quality of life for patients in some specific situations. Therefore, total artificial hearts may be considered medically necessary as a bridge to heart transplantation when policy criteria are met.

There is not enough research to show that total artificial hearts (TAHs) as destination therapy improves health outcomes for patients. Therefore, the use of TAHs as destination therapy is considered investigational.

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CODES

Note: There is no specific code for reporting prolonged extracorporeal percutaneous transseptal ventricular assist device; the appropriate code for reporting this procedure is 33999.

Codes	Number	Description
CPT	33927	Implantation of a total replacement heart system (artificial heart) with recipient cardiectomy
	33928	Removal and replacement of total replacement heart system (artificial heart)
	33929	Removal of a total replacement heart system (artificial heart) for heart transplantation (list separately in addition to code for primary procedure)
	33975	Insertion of ventricular assist device; extracorporeal, single ventricle
	33976	Insertion of ventricular assist device; extracorporeal, biventricular
	33977	Removal of ventricular assist device; extracorporeal, single ventricle
	33978	Removal of ventricular assist device; extracorporeal, biventricular
	33979	Insertion of ventricular assist device, implantable intracorporeal, single ventricle
	33980	Removal of ventricular assist device, implantable intracorporeal, single ventricular
	33981	Replacement of extracorporeal ventricular assist device, single or biventricular, pump(s), single or each pump
	33982	Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, without cardiopulmonary bypass
	33983	Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, with cardiopulmonary bypass

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Codes	Number	Description
	33990	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only
	33991	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transseptal puncture
	33992	Removal of percutaneous ventricular assist device at separate and distinct session from insertion
	33993	Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion
	33999	Unlisted procedure, cardiac surgery
	0451T	Insertion or replacement of a permanently implantable aortic counterpulsation ventricular assist system, endovascular approach, and programming of sensing and therapeutic parameters; complete system (counterpulsation device, vascular graft, implantable vascular hemostatic seal, mechano-electrical skin interface and subcutaneous electrodes)
	0452T	;aortic counterpulsation device and vascular hemostatic seal
	0453T	;mechano-electrical skin interface
	0454T	;subcutaneous electrode
	0455T	Removal of permanently implantable aortic counterpulsation ventricular assist system; complete system (aortic counterpulsation device, vascular hemostatic seal, mechano-electrical skin interface and electrodes)
	0456T	;aortic counterpulsation device and vascular hemostatic seal
	0457T	;mechano-electrical skin interface
	0458T	;subcutaneous electrode
	0459T	Relocation of skin pocket with replacement of implanted aortic counterpulsation ventricular assist device, mechano- electrical skin interface and electrodes
	0460T	Repositioning of previously implanted aortic counterpulsation ventricular assist device, subcutaneous electrode
	0461T	;aortic counterpulsation device
	0462T	Programming device evaluation (in person) with iterative adjustment of the implantable mechano-electrical skin interface and/or external driver to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable aortic counterpulsation ventricular assist system, per day
	0463T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable aortic counterpulsation ventricular assist system, per day
HCPCS	L8698	Miscellaneous component, supply or accessory for use with total artificial heart system
	Q0477 – Q0509	Ventricular assist device accessories, code range

Date of Origin: *January 1996*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 02

Heart Transplant

Effective: May 1, 2020

Next Review: March 2021
Last Review: March 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A heart transplant consists of replacing a diseased heart with a healthy donor heart. Transplantation is used for patients with refractory end-stage cardiac disease.

MEDICAL POLICY CRITERIA

I. Adult Patients

A. Human heart transplantation may be considered **medically necessary** for adults with end-stage heart failure (see Policy Guidelines) when one or more of the following accepted or probable indications is met:

Accepted Indications[1]

1. Hemodynamic compromise due to heart failure demonstrated by any one of the following:
   a. Maximal VO2 (oxygen consumption) <10 mL/kg/min with achievement of anaerobic metabolism
   b. Refractory cardiogenic shock
   c. Documented dependence on intravenous inotropic support to maintain adequate organ perfusion

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2. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or
3. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities.

Probable indications[1]

4. Maximal VO2 <14 mL/kg/min and major limitation of the patient's activities, or
5. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or
6. Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

II. Pediatric Patients

A. Human heart transplantation may be considered **medically necessary** in pediatric patients (see Policy Guidelines) when one of the following Criteria (1 or 2) are met:

1. There is a diagnosis of heart failure with persistent symptoms at rest and any one or more of the following Criteria (a-c) are met:
   a. Continuous infusion of intravenous inotropic agents; or
   b. Mechanical ventilatory support; or
   c. Mechanical circulatory support.

   OR

2. There is a diagnosis of pediatric heart disease with symptoms of heart failure in patients who do not meet Criteria II.A but any one of the following Criteria is met:
   a. Severe limitation of exercise and activity (if measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex); or
   b. Cardiomyopathies or previously repaired or palliated congenital heart disease, and significant growth failure attributable to the heart disease; or
   c. Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or
   d. Restrictive cardiomyopathy with reactive pulmonary hypertension; or
   e. Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or
   f. Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
   g. Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

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III. Human heart retransplantation after a failed primary heart transplant may be considered **medically necessary** in patients who meet criteria for heart transplantation.

IV. Human heart transplantation is considered **not medically necessary** when Criteria I or Criteria II is not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Adults with histories of congenital heart disease may be considered under applicable criteria for either Adult Patients (Criteria I) or Pediatric Patients (Criteria II).

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52
2. Heart/Lung Transplant, Transplant, Policy No. 03

BACKGROUND

In the United States, approximately 6.5 million people have heart failure and 309,000 die each year from this condition.[2] The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion. Heart transplantation can potentially improve both survival and quality of life in patients with end-stage heart failure.

Heart failure may be the consequence of a number of differing etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart defects. The leading indication for heart transplant has shifted over time from ischemic to non-ischemic cardiomyopathy. During the period 2009 to 2014, nonischemic cardiomyopathy was the dominant underlying primary diagnosis among patients 18-39 years (64%) and 40-59 years (51%) undergoing transplant operations. Ischemic cardiomyopathy was the dominant underlying primary diagnosis among the heart transplant recipients 60-69 years and 70 years and older, 50% and 55% respectively.[3] Overall, ischemic cardiomyopathy is the underlying heart failure diagnosis in approximately 40% of men and 20% of women who receive a transplant. Approximately 3% of the heart transplants during this time period were in adults with congenital heart disease.[4] The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body's needs under minimal exertion. Heart transplantation can potentially improve both survival and quality of life. According to the Organ Procurement and Transplant Network (OPTN), patient survival rate at one year is 87.5% in males and 85.6% in females and at five years is 72.4% in males and 67.4% in females.[5]

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The demand for heart transplants far exceeds the availability of donor organs, and the length of time patients are on the waiting list for transplants has increased.

According to data from the Organ Procurement and Transplantation Network, in 2019, a total of 3552 heart transplants were performed in the United States. As of March 16, 2020, there were 3646 patients on the waiting list for a heart transplant. [6] Also in recent years, advances in medical and device therapy for patients with advanced heart failure has improved the survival of patients awaiting heart transplantation. Due to the variable natural history of heart failure, functional and hemodynamic parameters have been utilized to estimate prognosis.

From 2008 to 2015, approximately 4% of heart transplants were repeat transplantations.[4] Heart retransplantation raises ethical issues due to the lack of sufficient donor hearts for initial transplants. The United Network for Organ Sharing (UNOS) does not have separate organ allocation criteria for repeat heart transplant recipients.

EVIDENCE SUMMARY

PRIORITIZATION OF CANDIDATES

The majority of heart transplant recipients are now hospitalized Status 1 patients at the time of transplant. This shift has occurred due to the increasing demand on the scarce resource of donor organs resulting in an increased waiting time for donor organs. Patients initially listed as a Status 2 candidates may deteriorate to a Status 1 candidate before a donor organ becomes available. At the same time, as medical and device therapy for advanced heart failure has improved, some patients on the transplant list will recover enough function to become delisted.

Johnson (2010) reported on waiting list trends in the U.S. between 1999 and 2008.[7] They noted an increasing trend of adult patients with congenital heart disease and retransplantation. The proportion of patients listed as Status 1 continued to increase, even as waiting list and post-transplant mortality for this group decreased. Meanwhile, Status 2 patients have decreased as a proportion of all candidates. Completed transplants have trended toward the extremes of age, with more infants and patients older than age 65 years having transplants in recent years. This is an update to what Lietz and Miller published in 2007, where they reported on patient survival on the heart transplant waiting list, comparing the era between 1990 and 1994 to the era of 2000 to 2005.[8] One year survival for UNOS Status 1 candidates improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared to 81.8% in the earlier time period.

As a consequence, aggressive treatment of heart failure has been emphasized in recent guidelines. Prognostic criteria have been investigated to identify patients who have truly exhausted medical therapy and thus are likely to derive the maximum benefit for heart transplantation. Maximal oxygen consumption (VO2), which is measured during maximal exercise, is one measure that has been suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology (ACC) has adopted maximal VO2 as one criterion for patient selection.[1] Studies have suggested that transplantation can be safely deferred in those patients with a maximal VO2 of greater than 14 mL/kg/min. The importance of the maximal VO2 has also been emphasized by an American Heart Association Scientific Statement addressing heart transplant candidacy.[9] In past years, a left ventricular ejection fraction (LVEF) of less than 20% or a New York Heart Association (NYHA) Class III or IV status may have been used to determine transplant

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candidacy. However, as indicated by the ACC criteria, these measurements are no longer considered adequate to identify transplant candidates. These measurements may be used to identify patients for further cardiovascular workup but should not be the sole criteria for transplant.

Methods other than maximal VO2 have been proposed as predictive models in adults.[10-13] The Heart Failure Survival Scale (HFSS) and Seattle Heart Failure Model (SHFM) are two examples. In particular, the SHFM provides an estimate of 1-, 2-, and 3-year survival with the use of routinely obtained clinical and laboratory data. Information regarding pharmacologic and device usage is incorporated into the model, permitting some estimation of effects of current, more aggressive heart failure treatment strategies. In 2006, Levy and colleagues[14] introduced the model using multivariate analysis of data from the PRAISE1 heart failure trial (n=1,125). Applied to the data of five other heart failure trials, the SHFM correlated well with actual survival (r: 0.98, standard error of the estimate=$\pm$3). The SHFM has been validated in both ambulatory and hospitalized heart failure populations[15-17] but with a noted underestimation of mortality risk, particularly in blacks and device recipients.[18,19] None of these models have been universally adopted by transplant centers.

INITIAL HEART TRANSPLANT

Survival after heart transplant

A systematic review by Almarsi (2019) was conducted to identify new variables associated with transplant outcomes that are not currently collected by the Organ Procurement and Transplantation Network (OPTN).[20] Eighty-one unique studies including 1,193, 410 transplant patients with median follow-up of 36 months posttransplant were included. Among the 108 unique risk factors identified, 104 were recipient-related and 4 were donor-related. The strongest relative association measure for a heart transplant outcome with a risk factor was 8.6 (recipient with the previous Fontan operation).

Nguyen (2017) investigated the benefit of heart transplantation compared with waiting list while accounting for the estimated risk of a given donor-recipient match among 28,548 heart transplant candidates in the OPTN between July 2006 and December 2015.[21] Net benefit from heart transplantation was evident across all estimates of donor-recipient status 1A and 1B candidates: status 1A (lowest-risk quartile hazard ratio [HR], 0.37; 95% CI, 0.31 to 0.43; highest-risk quartile HR=0.52; 95% CI, 0.44 to 0.61) and status 1B candidates (lowest-risk quartile HR=0.41; 95% CI, 0.36 to 0.47; highest-risk quartile HR=0.66; 95% CI, 0.58 to 0.74). Status 2 candidates showed a benefit from heart transplantation; however, survival benefit was delayed. For the highest-risk donor-recipient matches, a net benefit of transplantation occurred immediately for status 1A candidates, after 12 months for status 1B candidates, and after 3 years for status 2 candidates.

Lund (2016) examined the risk factors associated with 10-year posttransplant mortality among patients undergoing heart transplantation during 2000-2005 using the International Society for Heart and Lung Transplantation (ISHLT) Registry.[3] Markers of pretransplant severity of illness, such as pretransplant ventilator use (HR=1.35; 95% CI, 1.17 to 1.56; n=338), dialysis use (HR=1.51; 95% CI, 1.28 to 1.78; n=332), underlying diagnoses of ischemic (HR=1.16; 95% CI: 1.10 to 1.23; n=7822), congenital (HR=1.21; 95% CI, 1.04 to 1.42; n=456) or restrictive (HR=1.33; 95% CI, 1.13 to 1.58; n=315) heart disease (vs non-ischemic cardiomyopathy), and retransplant (HR=1.18; 95% CI, 1.02 to 1.35; n=489) were associated with post-transplant mortality risk at 10 years.

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Ting (2016) published a report that retrospectively evaluated outcomes of 134 patients one month to 78 years old (average 28) who received mechanical circulatory support for acute myocarditis with cardiogenic shock, between 1994 and 2014.[22] Patients recovering without a transplant were compared to those who received a transplant under mechanical circulatory support. 54% of patients survived on mechanical circulatory support, without transplant. Only 5% of the patients underwent transplant. The authors concluded transplant survival under mechanical circulatory support had favorable mid- and long-term outcomes.

Starling (2016) and Svobodova (2016) published studies evaluating transplant outcomes based on biomarkers and/or antibodies. Sterling published a one year observational, multicenter, cohort study in which 200 heart transplant patients were evaluated for biomarkers that could predict heart transplant outcomes.[23] Laboratory tests included anti-AHL antibody analysis, ELISPOT Panel of reactive T cell (PRT) assays, plasma angiogenesis-related proteins, peripheral blood and tissue gene expression profiling. Svobodova published a single-center retrospective study that evaluated antibody-mediated rejection (AMR).[24] Data was analyzed for pre- and post-transplant antibodies and antigens in transplant recipients and/or donors. Median follow-up was 39 months. Starling concluded it is still difficult to find reliable biomarkers that can determine heart transplant outcomes. Svobodova stated monitoring pre- and post-transplant antigens and antibodies may predict rejection.

According to the Organ Procurement and Transplantation Network (OPTN), Kaplan-Meier survival rates for heart transplants performed during 2008-2015 based on available U.S. data as of July 10, 2017, the 1-year survival after heart transplant was 90.5% (95% confidence interval [CI], 89.9% to 91.2%) and 91.1% (95% CI, 90.1% to 92.1%) for men and women, respectively. Three-year survival rates were 85.1% (95% CI, 84.3% to 86.0%) and 85.2% (95% CI, 83.8% to 86.4%) for men and women, respectively, and 5-year survival rates were 78.4% (95% CI, 77.3% to 79.3%) and 77.7% (95% CI, 76.0% to 79.2%), respectively.[5] Rana (2015) conducted a retrospective analysis of solid organ transplant recipients registered in the UNOS database from 1987 to 2012, including 54,746 patients who underwent a heart transplant.[25] Transplant recipients were compared with patients listed for transplant, but who did not receive a transplant after propensity score matching based on a variety of clinical characteristics. After matching, the median survival was 9.5 years in transplant recipients compared with 2.1 years in waiting list patients.

A 2013 study examined characteristics of patients who survived longer than 20 years after heart transplantation at a single center.[26] Thirty-nine heart transplant recipients who survived over 20 years post-transplant were compared to 98 patients who died between one and 20-years post-transplant. Independent factors associated with long-term survival were younger recipient age i.e., <45 years versus 45 years and older (OR: 3.9, 95% CI: 1.6-9.7) and idiopathic cardiomyopathy i.e. versus other etiologies (OR: 3.3, 95% CI: 1.4-7.8).

Bhama (2013) published results from study that reported on survival outcomes for heart transplantation in a cohort of adults with congenital heart disease (CHD) and identified risk factors for mortality that would help guide recipient and donor selection.[27] A retrospective analysis identified 19 patients that had transplantation for CHD and compared to 428 transplant patients that underwent transplantation for conditions other than CHD. There was no significant difference in survival (CHD vs control) at 30 days (89% vs 92%, p = 0.5567), one year (84% vs 86%, p = 0.6976), or five years (70% vs 72%, p = 0.8478). The only significant predictor of death in the CHD group was donor organ ischemic time >four hours

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(HR 13.26, 95% CI 1.3 to 132.2, p = 0.028). Authors suggested that adults with CHD have excellent early and mid-term survival after heart transplantation.

A 2012 study by Kalic analyzed prospectively collected data from the United Network for Organ Sharing (UNOS) registry.[28] The analysis included 9,404 individuals who had survived 10 years after heart transplant and 10,373 individuals who had died before 10 years. Among individuals who had died, mean survival was 3.7 years post-transplant. In multivariate analysis, statistically significant predictors of surviving at least 10 years after heart transplant included:

- Age younger than 55 years (odds ratio [OR]: 1.24, 95% confidence interval [CI]: 1.10 to 1.38),
- Younger donor age (OR: 1.01, 95% CI: 1.01 to 1.02),
- Shorter ischemic time (OR: 1.11, 95% CI: 1.05 to 1.18),
- White race (OR: 1.35, 95% CI: 1.17 to 1.56), and
- Annual center volume of nine or more heart transplants (OR: 1.31, 95% CI: 1.17 to 1.47).

Factors that significantly decreased the likelihood of 10-year survival in multivariate analysis included:

- Mechanical ventilation (OR: 0.53, 95% CI: 0.36 to 0.78), and
- Diabetes (OR: 0.67, 95% CI: 0.57 to 0.78).

Jalowiec (2011) compared clinical outcomes in sex-matched and sex-mismatched heart transplant recipients.[29] They retrospectively reviewed data from 347 heart transplant recipients; 237 (78.7%) received a heart from a same-sex donor, 40 (11.5%) cases involved a female donor and male recipient, and 34 (9.8%) cases involved a male donor and female recipient. There was not a statistically significant difference in the mortality rate during the first month post-transplant between the sex-matched and either sex-mismatched group. In adjusted analyses, two of the other nine study outcomes differed significantly among the three groups. The male donor-female recipient group had significantly more treated rejection episodes during the first year post-transplant and significantly more days of rehospitalization after the initial discharge than either of the other two groups. The incidence of steroid-induced diabetes, cardiac allograft vasculopathy, non-skin cancers, number of intravenous (IV)-treated infections post-transplant, and initial hospital length of stay were not significantly different among groups.

Pediatric considerations

The highest 1- and 3- year survival rate among pediatric patients undergoing heart transplant in the US, during 2008-2015, were 11-17 year old patients according to OPTN.[5] Patients younger than 1-year-olds had the lowest 1-, 3-, and 5-year survival among pediatric patients.

Rossano (2016) examined survival among pediatric heart transplant recipients using the ISHLT Registry. Among 12,091 pediatric patients undergoing heart transplantation during 1982-2014, the overall median survival was 20.7 years for infants, 18.2 years for children ages 1 to 5 years, 14.0 years for those ages 6 to 10 years, and 12.7 years for those ages 11 to 17 years. As the first year posttransplant represents the greatest risk for mortality, survival conditional on survival to 1 year was longer.[30]

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Kulkami (2016) published an evaluation of a multicenter prospective single ventricle reconstruction trial to determine outcomes of infant patients with a single ventricle who were listed for transplant after the Norwood procedure.[31] A public database was used to compare infants while on the waiting list and after transplant. Risk factors were also evaluated for those patients put on the waiting list for a transplant and for those who survived without a transplant. Of 555 patients 33 were listed and underwent transplant. One-year survival after being put on the waiting list, including those that died after transplant was 48%. Diagnosis for being put on the transplant list after the Norwood procedure, included worsening right ventricular function, non-hypoplastic left heart syndrome, and a complex intensive care unit stay. The authors determined patients having heart transplant as a rescue procedure within a year of the Norwood procedure had a higher risk of complications and mortality.

Garbern (2016) published a study that evaluated transplant outcomes for pediatric patients with myocarditis versus dilated cardiomyopathy (DCM).[32] During the study 137 children with myocarditis and 1,249 children with DCM underwent heart transplant. Data was taken from the Organ Procurement and Transplant Network (OPTN) database. The data for children with myocarditis was evaluated for a higher risk of mortality pre-transplant. The authors noted several study limitations including that they could not confirm data accuracy, but stated after the adjustment for severity of illness, children with myocarditis were not at a higher risk of mortality pre- and post-transplant than patients with DCM.

According to OPTN data, in 2015, 423 heart transplants were performed in children younger than 18 years of age.[6] Five-year survival rates by age group were: less than one year: 68.6% (95% CI, 62.0% to 75.1%); one to five years: 69.4% (95% CI, 64.1% to 74.7%); six to ten years: 73.1% (95% CI, 66.7% to 79.5%); and 11-17 years: 75.1% (95% CI, 72.6% to 77.5%).

A retrospective analysis of OPTN data focusing on the adolescent population was published by Savia in 2014.[33] From 1987 to 2011, 99 adolescents (age, 13-18) heart transplants were performed with myocarditis and 456 adolescents with coronary heart disease (CHD). Among adolescent transplant recipients with myocarditis, median graft survival was 6.9 years (95% CI, 5.6 to 9.6 years), which was significantly less than other age groups (i.e., 11.8 years and 12.0 years in younger and older adults, respectively). However, adolescents with CHD had a graft survival rate of 7.4 years (95% CI, 6.8 to 8.6 years), similar to that of other age groups.

According to the International Society for Heart and Lung Transplantation, 532 heart transplants in children younger than 18 years-old were reported worldwide in 2010.[34] This number compares to 543 reported in 2009. Among the pediatric transplants, about 25% were in infants younger than age one year, 37% were in children between the ages of one and 10 years, and 38% were in adolescents between the ages of 11 to 17 years. In infants, the most common indications for heart transplant were congenital heart disease (56%) and cardiomyopathy (40%). For children older than 10 years of age, the most common indication was cardiomyopathy (63%). Median survival has varied with age of the transplant recipient. Median survival was 19.2 years for infants, 15.6 years for one to 10 year-olds, and 11.9 years for 11-17 year-olds.

In 2011, a retrospective review of pediatric cardiac transplantation patients was published by Auerbach.[35] A total of 191 patients who underwent primary heart transplantation at a single center in the United States were included; their mean age was 9.7 years (range, 0 to 23.6 years). Overall graft survival was 82% at one year and 68% at five years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall patient survival was

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82% at one year and 72% at five years. In multivariate analysis, the authors found that congenital heart disease (HR: 1.6, 95% CI: 1.02-2.64) and requiring mechanical ventilation at the time of transplantation (HR: 1.6, 95% CI: 1.13-3.10) were both significantly independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small study group. Limitations of the study include that it was retrospective and conducted in only one center.

Patel (2010) presented a retrospective review of echocardiography and serum markers as a predictor of death or need for transplantation in newborns, children, and young adults with heart failure.[36] A total of 99 children with 139 admissions were evaluated on LVEF and tricuspid regurgitation, as well as on various serum markers for their predictive ability of death or need for transplantation in a stepwise multivariate Cox regression model. While brain natriuretic peptide (BNP) and tricuspid regurgitation were not predictive of need for transplantation, ejection fraction and lymphocytosis were predictive (ejection fraction odds ratio [OR]: 0.94, 95% CI: 0.90-0.98; for lymphocytosis, OR 5.40, 95% CI: 1.67–17.4). Serum levels of creatinine and sodium were also predictive. Clinical prediction rules based on these findings have not been compared to current strategies and await clinical validation.

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine if the pediatric heart allocation system, as revised in 1999, prioritizes patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices.[37] Of 3,098 children (younger than 18 years of age) listed between 1999 and 2006, a total of 1,874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1,943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that Status 1A patients are a heterogeneous population with large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included extracorporeal membrane oxygenation support (hazard ratio [HR]: 3.1), ventilator support (HR: 1.9), listing status 1A (HR: 2.2), congenital heart disease (HR: 2.2), dialysis support (HR: 1.9), and non-white race/ethnicity (HR: 1.7). The authors concluded that the pediatric heart allocation system captures medical urgency poorly, specific high-risk subgroups can be identified, and further research is needed to better define the optimal organ allocation system for pediatric heart transplantation.

HEART RETRANSPLANTATION

An analysis of OPTN data from 2008 to 2015 reported that 724 retransplants were performed (of 18,676 heart transplants, 3.9% of all transplants). Kaplan-Meier patient survival rates at 1, 3, and 5 years were lower among the retransplant recipients compared with primary transplant recipients.[5] An analysis of OPTN data from 1995 to 2012 reported that 987 retransplants were performed (of 28,464 heart transplants, 3.5% of all transplants).[38] Median survival among retransplant recipients was 8 years. The estimated survival at 1, 5, 10, and 15 years following retransplant was 80%, 64%, 47% and 30%, respectively. Compared with primary transplant recipients, retransplant patients had a somewhat higher risk of death (risk ratio [RR]=1.27, 95% CI, 1.13 to 1.42).

A number of studies have reviewed clinical experience with heart retransplantation in adults. In 2013, Saito published a retrospective review of data on 593 heart transplants performed at

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their institution; 22 of these (4%) were repeat transplantations.[39] The mean interval between initial and repeat transplant was 5.1 years. The indications for a repeat transplant were acute rejection in seven patients (32%), graft vascular disease in 10 patients (45%), and primary graft failure in five patients (23%). Thirty-day mortality after cardiac retransplantation was 32% (7 of 22 patients). Among patients who survived the first 30 days (n=15), 1-, 5- and 10-year survival rates were 93.3%, 79% and 59%, respectively. Comparable survival rates for patients undergoing primary cardiac transplants at the same institution (n=448) were 93%, 82% and 63%, respectively. An interval of one year or less between the primary and repeat transplantation significantly increased the risk of mortality. Three of nine patients (33.3%) with less than a year between the primary and retransplantation survived to 30 days. In comparison 12 of 13 patents (92%) with at least one year between primary and retransplantation were alive at 30 days after surgery.

Tjang (2008) published a systematic review of this literature that identified 22 studies reporting clinical outcomes of heart retransplantation in patients over 18 years old.[40] The most common indications for retransplantation were cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). The early mortality rate in individual studies was 16% (range: 5% to 38%). Some of the factors associated with poorer outcome after retransplantation were shorter transplant interval, refractory acute rejection, primary graft failure and an initial diagnosis of ischemic cardiomyopathy.

Topkara (2005) reviewed data on 766 adult patients who underwent heart transplantation between 1992 and 2002.[41] Forty-one (5%) of patients underwent repeat transplants; the indication for retransplantation was transplant-related coronary artery disease in 37 of 41 (90%) of these patients. Due to early experience with retransplantation, criteria at this institution were changed in 1993 so that patients with intractable acute rejection within 6 months of the initial transplant were ineligible for repeat transplants. One and five-year survival rates were 85.1% and 72.9%, respectively after primary transplantation and 72.2% and 47.5%, respectively after retransplantation. Survival rates were significantly lower in the retransplantation group, $p<0.001$. The authors did not report survival rates stratified by the length of time between initial and repeat transplantations.

Pediatric Considerations

As with initial heart transplants, children waiting for heart retransplantation have high waitlist mortality. Alsoufi (2015) published results from a retrospective analysis (1988 to 2013) that examined their experience with heart transplantations in pediatric patients with underlying congenital heart disease.[42] The study included sixteen patients who underwent primary heart transplantation. Participants were predominately male, and had a median age of 3.8 years. Competing risks analysis showed that at 10 years after heart transplantation, 13% of patients had undergone retransplantation, 43% of patients had died without retransplantation, and 44% of patients were alive without retransplantation. After retransplantation, 52% of patients were alive and 18% of patients had undergone a second retransplantation. Overall 15-year survival after initial heart transplantation was 41%. It is important to note this study has methodological considerations, which include but are not limited to, a small sample size; therefore, generalizability of results is limited.

Bock (2014) evaluated data on 632 pediatric patients who were listed for a heart retransplant at least one year (median, 7.3 years) after the primary transplant.[43] Patients' median age was four years at the time of the primary transplant and 14 years when they were relisted. Median

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waiting time was 75.3 days and mortality was 25.2% (159 of 632). However, waitlist mortality decreased significantly after 2006 (31% before 2006 and 17% after 2006, p<0.01).

Copeland (2014) published results from a retrospective chart review (n=183) and evaluated late survival among pediatric heart transplant patients, living for more than 15 years after transplant.[44]A total of 32 deaths were reported due to the following conditions: cardiac allograft vasculopathy (CAV); 11 (34.3%); posttransplant lymphoproliferative disease, 18.8%; acute rejection, 12.5%; sepsis, 6.3%; multiorgan failure, 3.1%; and unknown reasons, 25%. A total of 30 patients required cardiac retransplantation due to CAV. The authors concluded that heart transplantation in pediatric patients results in acceptable long-term survival. In patients who develop CAV and renal dysfunction, heart retransplantation is an acceptable form of palliative treatment.

Friedland-Little (2014) published results from a retrospective analysis (1985-2011) of pediatric and young adult survivors who had undergone repeat heart transplantations.[45] Patients were included in the review who had a primary heart transplant before the age of 21, and had undergone a third transplant. Patients were matched 1:3 with a control group of second heart transplant patients by age, era and re-transplant indication. The authors found no difference between third heart transplant patients (n=27) and the control second heart transplantation patients (n=79) with respect to survival (76% vs 80% at one year, 62% vs 58% at five years and 53% vs 34% at 10 years, p = 0.75). However, generalizability of the study's results may be limited due to methodological limitations, such as small sample size.

Mahle (2005) reviewed data from the United Network for Organ Sharing (UNOS) on heart retransplantation in patients less than 18 years old.[46] A total of 219 retransplantations occurring 1987 to 2004 were identified. The median age at initial transplant was 3 years old and the median age at retransplantation was nine years old. The median interval between initial procedure and retransplantation was 4.7 years. The most common indications for retransplantation were coronary allograft vasculopathy (n=111, 51%), non-specific graft failure (n=34, 18%) and acute rejection (n=19, 9%). Retransplantation was associated with worse overall survival than initial transplantation. One,five, and ten year survival rates were 83%, 70% and 58%, respectively after primary transplantation and 79%, 53% and 44%, respectively after retransplantation. The most common causes of death after retransplantation were acute rejection (14%), coronary allograft vasculopathy (14%) and infections (13%).

In both the adult and pediatric studies, poorer survival after retransplantation than initial transplantation is not surprising given that patients undergoing retransplantation experienced additional clinical disease or adverse events. The increased mortality from retransplantation appears to be mainly from increased short-term mortality. Longer-term survival rates after retransplantation seem reasonable, especially when patients with a higher risk of poor outcomes (e.g., those with a shorter interval between primary and repeat transplantation) are excluded. Also, patients with failed initial transplant have no other options besides a retransplantation.

POTENTIAL CONTRAINDICATIONS

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other

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disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Pretransplant malignancy is considered a relative contraindication for heart transplantation considering this has the potential to reduce life expectancy and could prohibit immune suppression after transplantation. However, with improved cancer survival over the years and use of cardiotoxic chemotherapy and radiotherapy, the need for heart transplantation has increased in this population,

Mistiaen (2015) conducted a systematic review to study the posttransplant outcome of pretransplant malignancy patients.[47] Most selected studies were small case series. Mean patient age varied from 6 years to 52 years. Hematologic malignancy and breast cancer were the most common type of pretransplant malignancies. Dilated, congestive, or idiopathic cardiomyopathy was mostly the common reason for transplantation in 4 case series, chemotherapy related cardiomyopathy was the most important reason for transplantation in the other series. Hospital mortality varied between 0% and 33%, with small sample size potentially explaining the observed variation, One large series reported similar short-term and long-term posttransplant survival of chemotherapy related (N=232) and other nonischemic cardiomyopathy (N=8890) patients. The 1-, 3-, and 5-year survival rates of were 86%, 79%, and 71% for patients with chemotherapy-related cardiomyopathy compared with 87%, 81%, and 74% for other transplant patients. Similar findings were observed for 1-year survival in smaller series. Two-, 5-, and 10-year survival rates among pretransplant malignancy patients were also comparable with other transplant patients. In addition to the nonmalignancy related factors such as cardiac, pulmonary, and renal dysfunction, two malignancy related factors were identified as independent predictors of 5-year survival. Malignancy-free interval (the interval between treatment of cancer and heart transplantation) of less than 1 year was associated with lower 5-year survival compared with a longer interval (<60% vs >75%). Patients with prior hematologic malignancies had an increased posttransplant mortality in three small series. Recurrence of malignancy was more frequent among patients with a shorter disease-free interval, 63%, 26%, and 6% among patients with less than 1 year, 1 to 5 years, and more than 5 years of disease-free interval, respectively.

Yoosabai (2015) conducted a retrospective review among 23,171 heart transplant recipient in the OPTN/UNOS database to identify whether pretransplant malignancy increases the risk of posttransplant malignancy.[48] Posttransplant malignancy was diagnosed in 2673 (11.5%) recipients during the study period. A history of any pretransplant malignancy was associated with increased risk of overall posttransplant malignancy (subhazard ratio [SHR], 1.51; p<0.01), skin (SHR=1.55, p<0.01), and solid organ malignancies (SHR=1.54, p<0.01) on multivariate analysis.

ISHLT guidelines have recommended to stratify each patient with pretransplant malignancy as to their risk of tumor recurrence and that cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The guideline also recommended that the specific amount of time to wait to transplant after neoplasm remission will depend on these factors and no arbitrary time period for observation should be used.

OLDER AGE

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Jamil (2017) conducted a retrospective study of age as it relates to primary graft dysfunction after heart transplantation.[49] Of the 255 heart transplants studied, 70 (27%) of recipients were 65 years and older and 185 were younger; there were no significant differences in post-transplant morbidity (all p>0.12) or at 1-year survival between groups (p=0.88). The incidence of moderate or severe primary graft dysfunction was lower among the older patients (6%) than in the younger (16%; p=0.037). Study limitations included the single-center design, lack of data on long-term survival, and the potential for selection bias in retrospective studies.

Cooper (2016) published a retrospective cohort study evaluating transplant outcomes in elderly patients, by using data from the United Network for Organ Sharing database. Data on three groups of patients 18-59, 60-69 and greater than or equal to 70 years of age were compared for five-year survival rates. The authors noted that patients greater than or equal to 70 had more ischemia and renal dysfunction than the 60-69 age group and received transplants from older donors who were more ill or had a history of drug abuse. Five-year survival rates were 26.9% for the 18-59 age group, 29.3% for the 60-69 age group, and 30.8% for the greater than or equal to 70 age group. The authors also noted limitations with this retrospective review including but not limited to potential risk of bias with patient transplant selection and quality of the data. The authors concluded the greater than or equal to 70 age group showed no significant difference in outcomes from the 60-69 age group and should not be excluded from receiving a transplant.

Awad (2016) reported on a single-center retrospective review of 704 adults who underwent heart transplantation from 1988 to 2012 to investigate the mortality and morbidity rates of heart transplantations among recipients 70 years of age and older (n=45) compared with recipients younger than 70 years (n=659).[50] The older and younger groups had similar 1-year (93.0 vs 92.1; p=0.79), 5-year (84.2 vs 73.4; p=0.18), and10-year (51.2 vs 50.2; p=0.43) survival rates, respectively.

Kilic (2012) analyzed data from the UNOS on 5,330 patients age 60 and older (mean age 63.7 years) who underwent heart transplantation between 1995 and 2004.[51] A total of 3,492 individuals (65.5%) survived to five years. In multivariate analysis, statistically significant predictors of five year survival included younger age (OR: 0.97, 95% CI: 0.95 to 1.00), younger donor age (OR: 0.99, 95% CI: 0.99-1.00), white race (OR: 1.23, 95% CI: 1.02 to 1.49), shorter ischemic time (OR: 0.93, 95% CI: 0.87-0.99), and lower serum creatinine (OR: 0.92, 95% CI: 0.87 to 0.98). In addition, hypertension, diabetes, and mechanical ventilation each significantly decreased the odds of surviving to five years. Patients with two or more of these factors had a 12% lower rate of five years survival than those with none of them.

Daneshvar (2011) examined data on 519 patients who underwent heart transplantation between 1988 and 2009 at a single institution, with a particular focus on survival differences by age group.[52] There were 37 patients who were at least 70 years-old (group 1), 206 patients between 60 and 69 years (group 2), and 276 patients younger than 60 years (group 3). Median survival was 10.9 years in group one, 9.1 years in group two, and 12.2 years in group three (non-significant difference among groups). The five-year survival rate was 83.2% in group one, 73.8% in group two, and 74.7% in group three.

PULMONARY HYPERTENSION

Findings of several studies published in 2012 and 2013 suggested that patients with pulmonary hypertension who successfully undergo treatment can subsequently have good outcomes after heart transplant.[53-56] For example, De Santo (2012) reported on 31

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consecutive patients who had been diagnosed with unresponsive pulmonary hypertension at baseline right heart catheterization.[53] After 12 weeks of treatment with oral sildenafil, right heart catheterization showed reversibility of pulmonary hypertension, allowing listing for heart transplant. Oral sildenafil treatment resumed following transplant. One patient died in the hospital. A right heart catheterization at three months post-transplant showed normalization of the pulmonary hemodynamic profile, thereby allowing weaning from sildenafil in the 30 patients who survived hospitalization. The reversal of pulmonary hypertension was confirmed at one year in the 29 surviving patients. Similarly, in a study by Perez-Villa (2013) , 22 patients considered high-risk for heart transplant due to severe pulmonary hypertension were treated with bosentan. After four months of treatment, mean pulmonary vascular resistance (PVR) decreased from 5.6 to 3.4 Wood units. In a similar group of nine patients who refused participation in the study and served as controls, mean PVR during this time increased from 4.6 to 5.5 Wood units. After bosentan therapy, 14 patients underwent heart transplantation and the one-year survival rate was 93%.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY, AND AMERICAN HEART ASSOCIATION

Guidelines from the American College of Cardiology Foundation and American Heart Association were updated in 2017.[57] Evaluation for heart transplantation was recommended for patients in whom heart failure is assessed as refractory based on New York Heart Association functional class III or IV (stage D) for heart failure after previous guideline-directed medical therapy, use of devices such as an implantable cardioverter defibrillator or a cardiac resynchronization therapy device, or surgical management.

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2016, The International Society for Heart and Lung Transplantation (ISHLT) updated their heart transplantation criteria in and made the following updates to their recommendations:[58]

- 1.2 Use of heart failure prognosis scores. Heart failure prognosis scores should be performed along with cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated one year survival as calculated by the Seattle Heart Failure Model (SHFM) of <80% or a Heart Failure Survival Score (HFSS) in the high/medium risk range should be considered as reasonable cut points for listing (Level of Evidence: C; primarily expert consensus opinion).
- 1.4.1 Age, obesity, and cancer as comorbidities and their implications for heart transplantation list.
    - Carefully selected patients >80 years of age may be considered for cardiac transplantation (Level of Evidence: C).
    - Pre-transplantation body mass index (BMI) >35kg/m^2 is associated with a worse outcome after cardiac transplantation. For such obese patients, it is reasonable to recommend weight loss to achieve a BMI of ≤ 35kg/m^2 before listing for cardiac transplantation (Level of Evidence: C).
- 1.4.2 Diabetes, Renal dysfunction, and peripheral vascular disease.
    - Diabetes with end-stage damage or persistent poor glycemic control (glycosylated hemoglobin >7.5% or 58 mmol/mol) despite optimal effort is a relative contraindication for transplant (Level of Evidence: C).

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    - Renal function should be assessed using estimated glomerular filtration rate (eFGR) or creatinine clearance under optimal medical therapy. It is reasonable to consider the presence of irreversible renal dysfunction (eGRF <30 ml/min1.73m2) as a relative contraindication for heart transplantation alone (Level of Evidence: C).
    - Clinically server symptomatic cerebrovascular disease may be considered a contraindication to transplantation when it's presences limits rehabilitation and revascularization is not a viable option (Level of Evidence: C).
- 1.5.3 Psychosocial evaluation. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. The benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia has not been established, has the potential for harm, and therefore, heart transplantation cannot be recommended for this sub-group of patients (Level of Evidence: C).
- 1.8 Retransplantation. Retransplantation is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Level of Evidence: C).

THE AMERICAN HEART ASSOCIATION

The American Heart Association (AHA) Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group stated in 2007 that, based on level B (non-randomized studies) or level C (consensus opinion of experts), heart transplantation is indicated for pediatric patients as therapy for the following indications:[59]

- Stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previous repaired or palliated congenital heart disease,
- Stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributed to heart disease, pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension,
- The guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, in patients with pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m2 and/or a transpulmonary pressure gradient >15 mm Hg if administration of inotropic support or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m2 or the transpulmonary gradient to <15 mm Hg.

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SUMMARY

There is enough research to show that heart transplantation can improve survival for certain pediatric and adult patients. Guidelines based on research recommend heart transplant for people with certain indications. Therefore, heart transplant may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that heart retransplantation can improve survival for certain pediatric and adult patients who have had a prior transplant. Guidelines based on research recommend heart retransplantation for people with certain indications. Therefore, heart retransplantation may be considered medically necessary in patients who meet the policy criteria.

There is not enough research to show that heart transplantation or retransplantation improves health outcomes for all other indications. Therefore, heart transplantation or retransplantation is considered not medically necessary for indications when the policy criteria are not met.

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60. BlueCross BlueShield Association Medical Policy Reference Manual "Heart Transplant " Policy No. 7.03.09

CODES

Codes	Number	Description
CPT	33940	Donor cardiectomy (including cold preservation)
	33944	Backbench standard preparation of donor cadaver heart allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation
	33945	Heart transplant, with or without recipient cardiectomy
HCPCS	None	

Date of Origin: *March 2013*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 03

Heart-Lung Transplant

Effective: May 1, 2020

Next Review: March 2021
Last Review: March 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The heart/lung transplantation involves a coordinated triple operative procedure consisting of procurement of a donor heart-lung block, excision of the heart and lungs of the recipient, and implantation of the heart and lungs into the recipient. A heart/lung transplantation refers to the transplantation of one or both lungs and heart from a single cadaver donor.

MEDICAL POLICY CRITERIA

I. Heart/lung *transplantation* may be considered **medically necessary** for carefully selected patients with end-stage cardiac and pulmonary disease including, but not limited to, one of the following diagnoses:
   A. Irreversible primary pulmonary hypertension with heart failure
   B. Nonspecific severe pulmonary fibrosis, with severe heart failure
   C. Eisenmenger complex with irreversible pulmonary hypertension and heart failure
   D. Cystic fibrosis with severe heart failure
   E. Chronic obstructive pulmonary disease with heart failure
   F. Emphysema with severe heart failure
   G. Pulmonary fibrosis with uncontrollable pulmonary hypertension or heart failure

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II. Heart/lung transplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

III. Heart/lung *retransplantation* after a failed primary heart/lung transplant may be considered **medically necessary** in patients with end-stage cardiac and pulmonary disease as described in Criterion I above.

IV. Heart/lung retransplantation is considered **not medically necessary** in patients without end-stage cardiac and pulmonary disease.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Ventricular Assist Devices and Total Artificial Hearts, Surgery, Policy No. 52
2. Heart Transplant, Transplant, Policy No. 02
3. Lung and Lobular Transplant, Transplant, Policy No. 08

BACKGROUND

Combined heart/lung transplantation is intended to prolong survival and improve function in patients with end-stage cardiac and pulmonary diseases. The majority of recipients have Eisenmenger syndrome (37%), followed by idiopathic pulmonary artery hypertension (28%) and cystic fibrosis (14%). Eisenmenger syndrome is a form of congenital heart disease in which systemic-to-pulmonary shunting leads to pulmonary vascular resistance. Eventually, pulmonary hypertension may lead to a reversal of the intracardiac shunting and inadequate peripheral oxygenation, or cyanosis.[1]

However, the total number of patients with Eisenmenger syndrome has been declining in recent years, as a result of corrective surgical techniques and improved medical management of pulmonary hypertension. Heart/lung transplants have not increased appreciably for other indications either, as it has become more common to transplant a single or double lung and maximize medical therapy for heart failure, rather than perform a combined transplant. In these, patient survival rates are similar to lung transplant rates. Bronchiolitis obliterans syndrome is a major complication; one, five, and 10-year patient survival rates are 68%, 50%, and 40%, respectively.[1]

In 2019, 45 individuals received heart/lung transplants in the United States. As of March 2020, there were 49 patients on the waiting list for heart/lung transplants.[2]

EVIDENCE SUMMARY

Due to the nature of the patient population requiring heart/lung transplantation, there were no

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randomized controlled trials (RCTs) comparing heart/lung transplant to alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, and immunosuppressive therapy and are not germane to this policy. The following is a summary of evidence based on registry data, case series, and expert opinion.

PATIENT SELECTION

Patients who are eligible for heart/lung transplantation can be listed under both the heart and lung allocation systems in the United States. In 2005, United Network for Organ Sharing (UNOS) changed the method by which lungs were allocated, from one based on length of time on the waiting list, to a system that incorporates the severity of the patient's underlying disease, as well as likelihood of survival.[3] However, it has been noted that the individual systems underestimate the severity of illness in patients with both end-stage heart and lung failure, and modification of the lung allocation score can be appealed for patients who meet the following criteria:

- Deterioration on optimal therapy
- Right arterial pressure greater than 15 mm Hg
- Cardiac index less than 1.8 L/min/m^2.

PEDIATRIC CONSIDERATIONS

A 2014 analysis of data from the Organ Procurement and Transplantation Network (OPTN) reported on indications for pediatric heart/lung transplantation.[4] The number of pediatric heart/lung transplants has decreased in recent years (i.e., 56 cases in 1993-1997; 21 cases in 2008-2013). The three most common indications for pediatric heart/lung transplant were primary pulmonary hypertension (n=55), congenital heart disease (n=37), and Eisenmenger syndrome (n=30). However, while 30 children received a heart/lung transplant for Eisenmenger syndrome through 2002, none were performed for this indication since then to the date of the analysis. Pediatric heart/lung transplants have also been performed for other indications including alpha1 antitrypsin deficiency, pulmonary vascular disease, cystic fibrosis, and dilated cardiomyopathy.

In 2012, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) reported on pediatric heart/lung transplant data collected through June 2011.[5] In recent years, the number of heart/lung transplant procedures in children has decreased, and the number of lung transplants has increased. There were no heart/lung transplants in infants between 2007 and the date of the study. Overall, survival rates after heart/lung transplants are comparable in children and adults (median half-life of 4.7 and 5.3 years, respectively). For pediatric heart/lung transplants that occurred between January 1990 and June 2010, the five-year survival rate was 49%. The two leading causes of death in the first year after transplantation were non-cytomegalovirus infection and graft failure. Beyond three years post-transplant, the major cause of death was bronchiolitis obliterans syndrome. An updated report on pediatric lung and heart-lung transplant from the same registry in 2014 did not include updated data on pediatric heart-lung transplants due to the small number of patients available.[6]

RETRANSPLANTATION

Repeat heart-lung transplant procedures have been performed; only three published studies were identified that reported on outcomes after repeat heart-lung transplants. In 2014, the

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ISHLT described outcomes after retransplantation as compared with primary transplantation, including identifying risk factors leading to retransplantation and both transplant-related morbidities and mortality after retransplantation.[7] The authors reviewed 9,248 primary transplants and 602 retransplants. After retransplantation, early time-related risk of mortality was similar to that after primary transplantation (HR 1.07; 95% CI, 0.92 to 1.25; p=0.40), but both late-phase time-related risk of mortality (HR 1.67; 95% CI, 1.40 to 1.99; p<0.001) and requirement of an additional graft (HR 1.69; 95% CI, 1.18 to 2.43; p=0.004) were higher. Long-term morbidities were significantly more common after retransplantation than with primary transplantation. The authors concluded that retransplantation after primary transplant in the pediatric age group, although feasible with similar early survival, is associated with decreased long-term survival and an increase in transplant-related morbidities.

Yusen (2014) reported outcomes for adult heart-lung transplants, with a focus on retransplantation, using data from the ISHLT Registry.[8] Thirty-three participating centers reported 75 adult heart-lung transplants in 2012, a decline from the peak year for heart-lung transplants (1989) during which 226 heart-lung transplants were performed. From 1982-2012, 90 adults had a first heart–lung retransplant after a previous heart–lung transplant. These 90 patients had a median survival of 0.3 year, with an unadjusted survival rate of 52%, 43%, 36%, and 27% at three months, one year, three years, and five years, respectively. Those who survived to one year had a conditional mean survival of 7.9 years.

Shuhaiber (2008) published results from a review of data from the UNOS registry.[9] The authors identified 799 primary heart-lung and 19 repeat heart-lung transplants. According to Kaplan-Meier survival analysis, the observed median survival times were 2.08 years after primary transplant and 0.34 years after repeat transplants. In addition, the authors analyzed survival data in matched pairs of primary and repeat transplant patients, who were matched on a number of potentially confounding demographic and clinical characteristics. Matches were not available for four repeat transplant patients. For the 15 repeat transplant patients with primary transplant matches, survival time did not differ significantly in the two groups. Being on a ventilator was statistically significantly associated with decreased survival time. The main limitation of this analysis is the small number of repeat transplant procedures performed.

POTENTIAL CONTRAINDICATIONS

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure, or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation (e.g., imminently terminal cancer or other disease). Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

Malignancy

Concerns regarding a potential recipients history of cancer were based on the observation of significantly increased incidence of cancer in kidney transplant patients.[10] In fact, carcinogenesis is two to four times more common, primarily skin cancers, in both heart transplant and lung transplant patients, likely due to the higher doses of immunosuppression

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necessary for the prevention of allograft rejection.[1,11] The incidence of *de novo* cancer in heart transplant patients approaches 26% at eight years post-transplant, the rate for lung transplant is 28% at ten years. For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.[12,13]

In a 2013 retrospective cohort study, *de novo* cancer-related deaths in Australian liver and cardiothoracic transplant recipients were analyzed during a median five year follow-up.[14] *De novo* cancer-related mortality risk in liver and cardiothoracic recipients was significantly elevated compared to the matched general population (n = 171; SMR = 2.83; 95% confidence interval [95%CI], 2.43-3.27). Excess risk was observed regardless of transplanted organ, recipient age group or sex. Risk of death from *de novo* cancer was high in pediatric recipients (n = 5; SMR = 41.3; 95%CI, 13.4-96.5), four of the five deaths were non-Hodgkin lymphoma. Authors suggest that *de novo* cancer was a leading cause of late death, particularly in heart and liver transplantation.

However, it should be noted that the availability of alternate treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage cardiopulmonary failure patients may not have an option. A small study (n=33) of survivors of lymphoproliferative cancers who subsequently received cardiac transplant had one, five, and ten-year survival rates of 77%, 64%, and 50%, respectively.[15] By comparison, overall one, five, and ten-year survival rates are expected to be 88%, 74%, and 55%, respectively for the general transplant candidate. The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients in whom cancer is thought to be cured should not be excluded from consideration for transplant. UNOS has not addressed malignancy in current policies.

HIV

Solid organ transplant for patients who are HIV-positive (HIV+) was historically controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity and the impact of immunosuppression on HIV disease. The availability of highly active antiretroviral therapy (HAART), has markedly changed the natural history of the disease. A 2009 retrospective case series reported favorable outcomes for seven patients with HIV who received a heart transplant.[16] However, there is little data directly comparing outcomes for patients with and without HIV or for combined heart-lung transplants

As of February 2013, the UNOS/OPTM policy on HIV-positive transplant candidates states: “A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy.”[2]

OTHER

Considerations for heart transplantation and lung transplantation alone may also pertain to combined heart-lung transplantation. For example, cystic fibrosis accounts for the majority of pediatric candidates for heart-lung transplantation, and infection with *Burkholderia* species is associated with higher mortality in these patients. Also, experience with kidney transplantation in patients infected with HIV in the era of HAART has opened discussion of

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transplantation of other solid organs in these patients. These topics are addressed more fully in the separate policies on heart transplantation and lung transplantation.

PRACTICE GUIDELINE SUMMARY

THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2015, the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation updated their 2006 their consensus-based guidelines [17,18] The guideline states:

> "Patients with advanced cardiac and lung diseases not amenable to either isolated heart or lung transplant may be candidates for combined heart-lung transplantation. Most commonly, patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH [pulmonary arterial hypertension] are considered for heart-lung transplantation."

The guidelines include criteria for absolute and relative contraindications, as well as special surgical and disease specific considerations for all types of organ transplants.

SUMMARY

There is enough research to show that heart/lung transplantation can improve survival for certain patients. Therefore, heart/lung transplant may be considered medically necessary in patients who meet criteria. Similarly, heart/lung retransplantation may improve survival for certain patients who have had a prior transplant. Therefore, heart/lung retransplantation may be considered medically necessary in patients with a failed prior transplant who meet the clinical criteria for heart-lung transplantation.

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CODES

Codes	Number	Description
CPT	33930	Donor cardiectomy-pneumonectomy, (including cold preparation)

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Codes	Number	Description
	33933	Backbench standard preparation of cadaver donor heart/lung allograft prior to transplantation, including dissection of allograft from surrounding soft tissues to prepare aorta, superior vena cava, inferior vena cava, and trachea for implantation
	33935	Heart-lung transplant with recipient cardiectomy-pneumonectomy
HCPCS	None	

Date of Origin: *March 2013*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 05

Liver Transplant

Effective: June 1, 2020

Next Review: March 2021
Last Review: April 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain, circulatory or cardiac death, or with a liver segment donation from a living donor. Patients are prioritized for transplant according to length of time on the waiting list, mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS).

MEDICAL POLICY CRITERIA

I. A liver transplant, using a cadaver or living donor, may be **medically necessary** for patients with irreversible, end-stage liver failure due to conditions that include, but are not limited to, the following:
   A. Cholestatic Liver Diseases
      1. Biliary atresia
      2. Familial cholestatic syndromes
      3. Primary biliary cirrhosis
      4. Secondary biliary cirrhosis

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5. Primary sclerosing cholangitis
6. Secondary sclerosing cholangitis when the primary etiology is resolved
7. Alagille syndrome
8. Nonsyndromic paucity of the intrahepatic bile ducts
9. Cystic fibrosis

B. Hepatocellular disease
1. Alcoholic cirrhosis
2. Viral hepatitis (including A, B, C, or non-A, non-B)
3. Autoimmune hepatitis
4. Cryptogenic cirrhosis
5. Alpha-1 antitrypsin deficiency
6. Hemochromatosis
7. Protoporphyria
8. Wilson's disease
9. Non-alcoholic steatohepatitis

C. Malignancies such as the following:
1. Primary hepatocellular carcinoma confined to the liver
2. Rare, non-hepatocellular malignancies originating in the liver such as hemangioepitheliomas in young adults and hepatoblastomas in children, and hemangioendotheliomas
3. Fibrolamellar hepatocellular carcinoma
4. Unresectable hilar cholangiocarcinoma

D. Vascular disease
1. Budd-Chiari syndrome (congenital hepatic vein thrombosis)
2. Veno-occlusive disease

E. Inborn errors of metabolism

F. Trauma and toxic reactions

G. Miscellaneous
1. Polycystic disease of the liver in patients who have massive hepatomegaly causing obstruction or functional impairment
2. Familial amyloid polyneuropathy (Corino de Andrade's disease, paramyloidosis)
3. Amyloidosis
4. Disorders of branch chain amino acids (e.g., Maple syrup urine disease (MSUD), branched chain a-ketoacid dehydrogenase (BCKD)
5. Fulminant hepatitic failure

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6. Glycogen storage disease type IV
7. Hyperoxaluria
8. Steatohepatitis
9. Tyrosinemia
10. Urea cycle defects

II. Liver transplantation is considered **not medically necessary** in the following patients:
   A. Patients with hepatocellular carcinoma that has extended beyond the liver.
   B. Patients with active alcohol and/or substance abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of three months is required.)

III. Liver transplantation is considered **investigational** in the following patients:
   A. Intrahepatic cholangiocarcinoma
   B. Patients with an extrahepatic malignancy, other than those noted above
   C. Patients with neuroendocrine tumors metastatic to the liver

IV. Liver retransplantation may be considered **medically necessary** in patients with one or more of the following diagnoses:
   A. Primary graft nonfunction
   B. Hepatic artery thrombosis
   C. Chronic rejection
   D. Ischemic type biliary lesions after donation after cardiac death
   E. Recurrent non-neoplastic disease-causing late graft failure

V. Liver retransplantation is considered **investigational** in all other situations not described above in criteria IV.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Small Bowel/Liver and Multivisceral Transplant, Transplant, Policy No. 18

BACKGROUND

RECIPIENTS

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In March 2019, OPTN and UNOS published its most recent allocation system.[1]

Status 1A Adults

1. The candidate is at least 18 years old at the time of registration
2. The candidate has a life expectancy without a liver transplant of less than 7 days and has at least *one* of the following conditions:
    a. Fulminant liver failure, without pre-existing liver disease and currently in the intensive care unit (ICU), defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease, and has at least *one* of the following criteria:
        i. Is ventilator dependent
        ii. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iii. Has an international normalized ratio (INR) greater than 2.0
    b. Anhepatic
    c. Primary non-function of a transplanted whole liver within 7 days of transplant, with aspartate aminotransferase (AST) greater than or equal to 3,000 U/L and at least *one* of the following:
        - International normalized ratio (INR) greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25
        - Lactate greater than or equal to 4 mmol/L

    All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

    d. Primary non-function within 7-days of transplant of a transplanted liver segment from a deceased or living donor, evidenced by at least *one* of the following:
        - INR greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25
        - Lactate greater than or equal to 4 mmol/L
    e. Hepatic artery thrombosis (HAT) within 7-days of transplant, with AST greater than or equal to 3,000 U/L and at least *one* of the following:
        - INR greater than or equal to 2.5
        - Arterial pH less than or equal to 7.30
        - Venous pH less than or equal to 7.25
        - Lactate greater than or equal to 4 mmol/L

    All laboratory results reported for the tests required above must be from the same blood draw taken 24 hours to 7 days after the transplant.

    Candidates with HAT in a transplanted liver within 14 days of transplant not meeting the above criteria will be listed with a MELD of 40.

    f. Acute decompensated Wilson's disease

Status 1A Pediatrics

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning

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18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.

2. The candidate has at least *one* of the following conditions:
    a. Fulminant liver failure without pre-existing liver disease, defined as the onset of hepatic encephalopathy within 56 days of the first signs and symptoms of liver disease and has at least *one* of the following criteria:
        i. Is ventilator dependent
        ii. Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iii. Has an international normalized ratio (INR) greater than 2.0
    b. Diagnosis of primary non-function of a transplanted liver within 7 days of transplant, evidenced by at least *two* of the following:
        i. Alanine aminotransferase (ALT) greater than or equal to 2,000 U/L
        ii. INR greater than or equal to 2.5
        iii. Total bilirubin greater than or equal to 10 mg/dL
        iv. Acidosis, defined as *one* of the following:
            - Arterial pH less than or equal to 7.30
            - Venous pH less than or equal to 7.25
            - Lactate greater than or equal to 4 mmol/L

    All laboratory results reported for any tests required for the primary non-function of a transplanted liver diagnosis above must be from the same blood draw taken between 24 hours and 7 days after the transplant.

    c. Diagnosis of hepatic artery thrombosis (HAT) in a transplanted liver within 14 days of transplant
    d. Acute decompensated Wilson's disease

Status 1B patients

1. The candidate is less than 18 years old at the time of registration. This includes candidates less than 18 years old at the time of registration, who remain on the waiting list after turning 18 years old, but does not include candidates removed from the waiting list at any time who then return to the waiting list after turning 18 years old.
2. The candidate has *one* of the following conditions:
    a. The candidate has a biopsy-proven hepatoblastoma without evidence of metastatic disease.
    b. The candidate has an organic acidemia or urea cycle defect and a MELD or PELD exception score of 30 points for at least 30 days.
    c. Chronic liver disease with a calculated MELD greater than 25 for adolescent candidates 12 to 17 years old, or a calculated PELD greater than 25 for candidates less than 12 years old, and has at least *one* of the following criteria:
        i. Is on a mechanical ventilator
        ii. Has gastrointestinal bleeding requiring at least 30 mL/kg of red blood cell replacement within the previous 24 hours
        iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.

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d. Chronic liver disease and is a combined liver-intestine candidate with an adjusted MELD or PELD score greater than 25 according to *Policy 9.1.F: Liver-Intestine Candidates* and has at least *one* of the following criteria:
    i. Is on a mechanical ventilator
    ii. Has gastrointestinal bleeding requiring at least 10 mL/kg of red blood cell replacement within the previous 24 hours
    iii. Has renal failure or renal insufficiency requiring dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
    iv. Has a Glasgow coma score (GCS) less than 10 within 48 hours before the status 1B assignment or extension.

Following Status 1, donor livers will be prioritized to those with the highest scores on MELD (model for end-stage liver disease) or PELD (pediatric end-stage liver disease). MELD and PELD are a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (i.e., INR) and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Aside from Status 1, donor livers are prioritized to those with the highest MELD or PELD number; waiting time is only used to break ties among patients with the same MELD or PELD score and blood type compatibility. In the previous system, waiting time was often a key determinant of liver allocation, and yet waiting time was found to be a poor predictor of the urgency of liver transplant, since some patients were listed early in the course of their disease, while others were listed only when they became sicker. In the revised allocation system, patients with a higher mortality risk and higher MELD/PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer.[2]

DONORS

Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, the term “split grafts” refers to dividing a donor liver into two segments that can be used for two recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and pediatric populations from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe, or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively, shortens the preservation time for the donor liver, decreases disease transmission and allows time to optimize the recipient's condition pretransplant.

EVIDENCE SUMMARY

Relevant outcomes for studies on liver transplantation (LT) include waiting time duration, dropout rates, survival time, and recurrence. As experience with LT has matured, patient selection criteria have broadened to include a wide variety of etiologies. The most controversial etiologies include viral hepatitis and primary hepatocellular cancer. In particular, the presence of hepatitis B virus (HBV) and hepatitis C virus (HCV) has been a controversial indication for LT because of the high potential for recurrence of the virus and subsequent recurrence of liver disease. However, registry data indicate that the long-term survival rate (seven years) for HBV positive transplant recipients is 47%, which is lower than that seen in other primary liver

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diseases such as primary biliary cirrhosis (71%) or alcoholic liver disease (57%).[2] Recurrence of HCV infection in transplant recipients has been nearly universal and 10 to 20% of patients will develop cirrhosis within five years.[3] Although these statistics raise questions about the most appropriate use of a scarce resource (donor livers), the long-term survival rates are significant in a group of patients who have no other treatment options. In the past, the long-term outcomes in patients with primary hepatocellular malignancies were poor (19%) compared to the overall survival of LT recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of five cm or less, or up to three tumors that are three cm or smaller and without extrahepatic spread or macrovascular invasion), has dramatically improved overall survival rates. In a systematic review of LT for hepatocellular carcinoma (HCC), Maggs (2012) found five-year overall survival rates ranged from 65% to 94.7% in reported studies.[4] Transplant represents the only curative approach for many of these patients who present with unresectable organ-confined disease and expansion of patient selection criteria. Bridging to transplant, or down-staging of disease, to qualify for LT is frequently studied. Finally, LT cannot be considered curative in patients with locally extensive or metastatic liver cancer, or in patients with isolated liver metastases with extrahepatic primaries.[2]

LIVING DONOR LIVER TRANSPLANTATION: DONOR OUTCOMES

Due to the scarcity of donor organs and the success of living donation, LDLT has become accepted practice. The living donor undergoes hepatectomy of the right lobe, left lobe, or left lateral segment, which is then transplanted into the recipient. Since right hepatectomy involves the resection of 60% to 70% of the total volume of the donor liver, the safety of the donor has been the major concern. The surgical literature suggests that right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia appears to have the most extensive experience and has reported the results of their first 40 adult-to-adult LDLTs, performed between June 1998 and October 1999.[5] There were an equal number of related and unrelated donors. Minor complications occurred in seven donors. The outcomes among recipients were similar to those associated with cadaveric donor livers performed during the same period of time. However, in the initial series of 20 patients, four out of five deaths occurred in recipients who were classified as 2A. In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living donor transplant. Other case series have reported similar success rates.[6-8]

Tokodai (2016) published a retrospective review of 56 patients who underwent hepatectomy, between April 2001 and August 2010.[9] Donors were classified as under 50 (average 32) or greater than or equal to 50 (average 58) years of age. The one-, three-, and five-year graft survival rates were 80%, 60%, and 50%, respectively, in the greater than or equal to 50 years of age group compared to the under 50 years of age group with survival rates of 89%, 87%, and 82%. The authors concluded older patients can undergo hepatectomy safely, but have longer hospital stays and grafts do not survive as long.

Brown (2013) reported on the results of a survey focusing on adult living-related recipients in the United States.[10] The following statistics were reported:

- The survey encompassed 449 adult-to-adult transplantations
- Half of the responding programs already had performed at least one adult-to-adult LDLT, and 32 of the remaining 41 centers were planning to initiate such surgery

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- 14 centers had performed more than 10 such transplantations, and these centers accounted for 80% of these transplants
- A total of 45% of those evaluated for living donation subsequently donated a liver lobe; 99% were genetically or emotionally related to the recipient
- Complications in the donor were more frequent in the centers that performed the fewest living-related donor transplantations
- There was one death among the donors, but complications were relatively common (i.e., biliary complications) in 6% and reoperation in 4.5%

Reports of several donor deaths re-emphasize the importance of careful patient selection based in part on a comprehensive consent process and an experienced surgical team.[11-13] In December 2000, the National Institutes of Health convened a workshop on LDLT. A summary of this workshop was published in 2002.[14] According to this document, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2% to 0.5%. Based on survey results, the workshop reported that donor morbidity was common: 7% required re-exploration, 10% had to be re-hospitalized, and biliary tract complications occurred in 7%. The median complication rate reported by responding transplant centers was 21%. The summary report concluded that the incidence and type of complications encountered, and the mortality associated with LDLT in both donors and recipients needs to be determined and compared with that for patients undergoing cadaveric transplantation.

Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for hepatectomy must be voluntary and free of coercion; therefore, it was preferable that the donor have a significant long-term and established relationship with the recipient. According to the workshop summary, "At the present time, nearly all centers strive to identify donors who are entirely healthy and at minimal risk during right hepatectomy. As a result, only approximately one third of persons originally interested in becoming a living liver donor complete the evaluation process and are accepted as candidates for this procedure."

Criteria for a recipient of a living-related liver are also controversial, with some groups advocating that living-related donor livers be used only in those most critically ill, while others state that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival.[14]

In 2000 the American Society of Transplant Surgeons issued the following statement:[15]

"Living donor transplantation in children has proven to be safe and effective for both donors and recipients and has helped to make death on the waiting list a less common event. Since its introduction in 1990, many of the technical and ethical issues have been addressed and the procedure is generally applied.

The development of left or right hepatectomy for adult-to-adult living donor liver transplantation has been slower. Because of the ongoing shortage of cadaver livers suitable for transplantation, adult-to-adult living donor liver transplantation has been undertaken at a number of centers. While early results appear encouraging, sufficient data is not available to

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ascertain donor morbidity and mortality rates. There is general consensus that the health and safety of the donor is and must remain central to living organ donation."

LIVING DONOR VERSUS DECEASED DONOR LIVER TRANSPLANT: RECIPIENT OUTCOMES

Few high-quality studies are available regarding recipient outcomes based upon direct comparison of liver transplantation from living and deceased donors.

A systematic review by Gavrilidis (2019) evaluated differences in outcomes between recipients of living-related adult donor and recipients of split liver transplantation from deceased donors.[16] A meta-analysis revealed differences in age distributions for both donors and recipients, with LDLT donors tending to be older than split donors (mean difference 11.12 years, p<0.001) and LDLT recipients tending to be younger than split transplant recipients (mean difference 2.06 years, p<0.001). However, there were no significant differences in postoperative complications, graft survival or overall survival between groups.

Humar (2019) compared outcomes between LDLT (n=245) and DDLT (n=592) at a single center in the U.S. between 2009 and 2019[17] The authors reported superior three-year survival in LDLT recipients (86% vs. 80% for DDLT, p=0.03), as well as shorter hospital stays (11 vs. 13 days, p=0.03) lower likelihood of intraoperative blood transfusion (52% vs 78%, p<0.01) or need for posttransplant dialysis (1.6% vs 7.4%, p<0.01). No significant differences were seen for early reoperation and biliary/vascular complication rates.

Wong (2019) published a retrospective intention-to-treat (ITT) analysis with propensity score matching comparing living and deceased donor LT.[18] The study included data for 375 patients listed for LT between 1995 and 2014: 188 patients in the ITT-DDLT group, and 187 in the ITT-LDLT group. Of these, 122 patients on the DDLT waitlist and 27 on the LDLT waitlist were delisted. Overall survival at one-, three- and five-years was significantly better in the ITT-LDLT group (94.1 vs. 77.5%, 81.4 vs. 48.7% and 75.9 vs. 40.8%, respectively). After propensity score matching, overall and recurrence-free survival were similar between groups.

Przybyszerski (2018) compared outcomes after LDLT and deceased donor liver transplant (DDLT) in a retrospective cohort of pediatric patients.[19] A total of 241 children were included in the study (DDLT n=177, LDLT n=64). Most of the LDLT donors were haplo-identical parents. The study found that LDLT was generally associated with better outcomes than deceased donor LT, including a lower rate of acute cellular rejection (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.29 to 0.98, p=0.04), chronic rejection (HR 0.12, 95% CI 0.03 to 0.56. p=0.007), and graft loss (HR 0.29, 95% CI 0.10 to 0.88, p=0.03). No difference in mortality by graft type was seen.

Samstein (2017) published a cohort study evaluating complications for recipients receiving DDLT versus LDLT (LDLT).[20] Patients in the study received DDLT (n=471) or LDLT (n=565) from 1998 to 2010, and were followed for up to 10 years post-transplant. The DDLT recipients were found to have higher occurrences of hepatocellular carcinoma, ascites, intra-abdominal bleeding, cardiac complications and pulmonary edema. The LDLT patients had higher biliary-related complications, hepatic artery thrombosis and chronic kidney disease. There was no difference in resolution time, for either group. The authors concluded LDLT outcomes are better than with DDLT, but improvements are needed to lessen complications for both LDLT and DDLT.

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Ushigome (2016) published a study evaluating living donor transplants for patients over 60 years of age.[21] Seventy-six adult patients were divided into a greater than 60 years of age group (n=21) or a less than 60 years of age group (n=55). The one-, three-, five-, and 10-year survival rates for the greater than 60 years of age group were 89.9%, 89.9%, 83.0%, and 83.0%, respectively, compared to the less than 60 years of age group with survival rates of 91.1%, 85.2%, 82.8%, and 82.9%. The authors reported no significant differences between the groups' survival rates but noted that the elderly transplant recipients were frailer and needed careful management.

Olthoff (2015) published results from a prospective multicenter National Institutes of Health study comparing recipient outcomes and associated risks from LDLT and DDLT.[22] This was the same cohort evaluated by Samstein (2017), described above. Mortality and graft failure for 1427 liver recipients (963 LDLT and 464 DDLT) enrolled in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study who received transplant between 1998 and 2013, at one of twelve North American centers were analyzed at long-term follow-up (median of 6.7 years). Probability of survival at 10 years was higher for recipients of LDLT then DDLT (70% vs. 64%, respectively). For survival, the adjusted hazard ration for recipients of LDLT was 0.98. LDLT recipients had lower mean model for end-stage liver disease compared to deceased donor recipients (15.5 vs. 20.4, respectively) and had better post-transplant outcomes, regardless of type of donated lobe.

Al Sebayel (2015) published results from a single-center retrospective analysis of survival of recipients of LDLT compared to DDLT in relation to their MELD score.[23] Data was assessed from 222 patients for LDLT and 269 patients with deceased donors. HCV recurrence as a cause of death was significantly higher in recipients of LDLT (p=0.023), but the mortality after one year was significantly higher in recipients of DDLT, (p=0.0072). Overall one, three and five-year survival rates of recipients of LDLT and DDLT were 89%, 85%, and 84%, respectively, for MELD score below 25, and 80%,78%, and 77%, respectively, for MELD score greater than or equal to 25. There were no significant differences in survival of recipients of LDLT and those of deceased donors, regardless of MELD score.

Grant (2013) reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between living donor liver transplants and deceased donor liver transplants for HCC.[24] For disease-free survival after living donor liver transplantation, the combined HR was 1.59 (95% CI 1.02 to 2.49) compared to deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality. Further study is needed to determine any differences between living and deceased liver transplantation outcomes for various etiologies.

MALIGNANCIES

The following two issues were the focus of the literature review regarding liver transplant for malignancy: 1) whether selection criteria for hepatocellular carcinoma should be expanded and 2) whether extrahepatic cholangiocarcinoma should be considered an acceptable indication for liver transplantation.

Hepatocellular Carcinoma

Selection Criteria for Hepatocellular Carcinoma

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The patient selection criteria for liver transplantation for hepatocellular carcinoma (HCC) have focused mainly on the number and size of tumors. An editorial by Llovet (2006) noted that the Milan criteria are considered the gold standard.[25] The Milan criteria specify that patients may either have a solitary tumor with a maximum tumor diameter of five cm or less, or up to three tumors three cm or smaller. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. UNOS adopted the Milan criteria, combined with one additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. A 2001 paper from the University of California, San Francisco (UCSF), proposed expanded criteria to include patients with a single tumor up to 6.5 cm in diameter, three or fewer tumors with maximum size 4.5 cm and a total tumor size of less than or equal to eight cm.[26] It should be noted that either set of criteria can be applied preoperatively with imaging or with pathology of the explanted liver at the time of intended transplant. Preoperative staging often underestimates what is seen on surgical pathology. To apply pathologic criteria a backup candidate must be available in case preoperative staging is inaccurate. Given donor organ scarcity, any expansion of liver transplant selection criteria has the potential to prolong waiting times for all candidates. Important outcomes in assessing expanded criteria include waiting time duration, death or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence or related outcomes such as disease-free survival. Survival time can be estimated beginning when the patient is placed on the waiting list using the intention-to-treat principal or at the time of transplantation. Llovet (2006) stated that one-year dropout rates for patients meeting Milan criteria are 15% to 30%, and five-year survival rates not reported by intention-to-treat should be adjusted down by 10% to 15%.

Guiteau (2010) reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4.[27] On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of one lesion less than six cm, equal to or less than three lesions, none greater than five cm and total diameter less than nine cm. Patient, allograft and recurrence-free survival at three years did not differ significantly between patients meeting Milan criteria versus patients under the expanded criteria (72.9% and 77.1%, 71% and 70.2%, and 90.5% and 86.9%, respectively). While preliminary results showed similar outcomes when using expanded Milan criteria, the authors noted their results were influenced by waiting times in Region 4 and that similar outcomes may be different in other regions with different waiting times. Additionally, the authors noted that an HCC consensus conference report on liver allocation in HCC patients does not recommend expanding Milan criteria nationally and encourages regional agreement.[28] The report addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF or other criteria.

Schwartz (2008) argued that selection based exclusively on the Milan criteria risks prognostic inaccuracy due to the diagnostic limitations of imaging procedures and the surrogate nature of size and number of tumors.[29] They predict that evolution of allocation policy will involve the following:

1. The development of a reliable prognostic staging system to help with allocation of therapeutic alternatives;
2. New molecular markers that might improve prognostic accuracy;

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3. Aggressive multimodality neoadjuvant therapy to downstage and limit tumor progression before transplant and possibly provide information about tumor biology based on response to therapy; and,
4. Prioritization for transplantation should consider response to neoadjuvant therapy, time on waiting list, suitability of alternative donor sources.

A limited body of evidence is available for outcomes among patients exceeding Milan criteria but meeting UCSF criteria (see table below). The largest series was conducted in 14 centers in France including an intention-to-treat total of 44 patients based on preoperative imaging at the time of listing, and a subset of 39 patients meeting pathologic UCSF criteria.[30] The median waiting time was 4.5 months, shorter than the typical six to twelve months in North America. Dropouts composed 11.4%. The post-transplant overall patient five-year survival of 63.6% was more favorable than the intention-to-treat probability of 45.5% but less favorable than among larger numbers of patients meeting Milan criteria. Similar findings were seen for disease-free survival and cumulative incidence of recurrence. Three centers in Massachusetts included ten patients beyond pathologic Milan criteria but within UCSF criteria.[31] Two-year survival post-transplant was 77.1%, with two patients dying and eight alive after a median of 32 months. A group of 74 patients meeting preoperative Milan criteria had a two-year survival probability of about 73%, but it is inadvisable to compare different preoperative and pathologic staging criteria.

From the series of patients from which the expanded UCSF criteria was developed, 14 satisfied those criteria on pathology but exceeded the Milan criteria.[32] UCSF investigators did not provide survival duration data for this subgroup but noted that two patients died. Although the French series suggested that outcomes among patients exceeding Milan criteria and meeting UCSF criteria are worse than for patients meeting Milan criteria, it is unclear if the latter group still achieves acceptable results. A benchmark of 50% five-year survival has been established in the liver transplant community. The French study met this by post-transplant pathologic staging results (63.6%) and fell short by preoperative intention-to-treat results (45.5%). United States centers have published data for only 24 patients exceeding Milan criteria and meeting UCSF criteria; survival and recurrence data are very sparse. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF criteria.

Several groups have worked on identifying predictors of survival and recurrence of disease. Ioannou (2008) analyzed UNOS data pre- and post-adoption of the MELD allocation system finding a six-fold increase in recipients with hepatocellular carcinoma and that survival in the MELD era was similar to survival to patients without HCC.[33] The subgroup of patients with larger (three to five cm) tumors, serum alpha-fetoprotein level equal to or greater than 455 mg/mL, or a MELD score equal to or greater than 20, however, had poor transplantation survival. A cancer recurrence prediction scoring system was developed by Chan (2008), based on a retrospective review and analysis of liver transplants at two centers to determine factors associated with recurrence of HCC.[34] Of 116 patients with findings of hepatocellular carcinoma in their explanted livers, 12 developed recurrent hepatocellular carcinoma. Four independent significant explant factors were identified by stepwise logistic regression: size of one tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, and the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds ratio. The accuracy of the method was confirmed in two validation cohorts.

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Table 1. Outcomes Among Patients with Hepatocellular Carcinoma Exceeding Milan Selection Criteria and Meeting UCSF Criteria

Study	Outcome	Group	Probability (%)			
			n	1yr	2yr	5yr
Decaens (2006)[30] 14 centers in France, Meeting Milan criteria (Milan+). Exceeding Milan criteria, meeting UCSF criteria (Milan-/UCSF+)	Intention-to-treat, preoperative					
	Overall patient survival	Milan+	279			60.1
		Milan-/UCSF+	44			45.5
	Cumulative incidence of recurrence	Milan+				20.2
		Milan-/UCSF+				27.1
	Disease-free survival	Milan+				60.4
		Milan-/UCSF+				47.8
	Post-transplant, pathologic (p)					
	Overall patient survival	pMilan+	184			70.4
		pMilan-/pUCSF+	39			63.6
	Cumulative incidence of recurrence	pMilan+				9.4
		pMilan-/pUCSF+				16.5
	Disease-free survival	pMilan+				7.02
		pMilan-/pUCSF+				62.7
	Milan-/UCSF+ median waiting time 4.5 mo (0.1-20.4); 5/44 dropouts (11.4%)					
Sotiropoulos (2006)[35] Essen, Germany. Unclear if criteria preoperative or pathologic.	Milan-/UCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo.					
Leung (2004)[31] 3 centers in Massachusetts, Meeting preoperative Milan criteria (Milan+)	Post-transplant overall patient survival	Milan+	74	85.9	~73	50.9
		pMilan-/pUCSF+	10		77.1	
	2 patients died at 3 and 22 months, 8 patients alive after median 32 mo follow-up (6.6-73.5)					
Yao (2002)[32] University of California, San Francisco	Post-transplant overall patient survival	pMilan+	46	91	81	72
	pMilan-/pUCSF+, n=14, 2 patients died, 8 alive but no information on survival duration, 1 patient retransplanted 5 mo after initial transplant					

The use of extended Milan criteria, to include other factors, has recently become an area of investigation. Tosco (2015) conducted a prospective study that recruited 233 patients with HCC according to their proposed total tumor volume (TTV, ≤115 cm^3)/alpha-fetoprotein (AFP, ≤400 ng/mL) score.[36] The Milan group was modified to include only patients with AFP <400 ng/mL (n=195); these patients were compared to patients beyond Milan, but within TTV/AFP (n=38), with an average follow-up of 34 ± 25 months. Risk of dropout was higher for patients beyond Milan (42.1%), than for those within Milan (25.1%, p = 0.033), and intent-to-treat survival was lower in patients beyond Milan (53.8% vs. 71.6% at four years, p<0.001). Post-transplant, patients within Milan criteria and those beyond Milan had similar recurrence rates (4.5% vs. 9.4%, p=0.138) and post-transplant survivals (78.7% vs. 74.6% at four years, p=0.932). The investigators concluded that expanding the Milan criteria may lead to increased risk of drop-out but does not impact overall post-transplant survival.

Liver Transplantation versus Liver Resection for Hepatocellular Carcinoma

Liver transplantation is the gold standard treatment for HCC meeting Milan criteria in decompensated livers such as Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is generally used for early HCC in livers classified as Child-Pugh class A.[37] Additionally, current UNOS criteria indicate a liver transplant candidate must not be eligible for resection.[1] However, the best treatment approach for early HCC in well-compensated livers is controversial.

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Schoenberg (2017) published a systematic review and meta-analysis of 54 retrospective studies (n=13,794) comparing liver resection (n=7,990) with transplantation (n=5,804) in patients with HCC.[38] At one-year follow-up, survival rates were higher in those receiving resection (86.17%) than in those receiving liver transplant (80.58%) (OR 1.19, 95% CI 0.99 to 1.43, p=0.07). At five-year follow-up, survival rates were better for those who received transplantation (61.26%) than for those receiving surgery (51.9%, OR 0.62, 95% CI 0.50 to 0.76, p<0.001). When a subgroup of patients with early HCC (eight studies) was analyzed, one-year follow-up showed comparable survival rates between surgically-treated patients (92.14%), and transplanted patients (90.38%) (OR 0.97, 95% CI 0.63 to 1.50, p=0.89). At five years, transplanted patients had a significantly higher survival rate (66.67%) than surgically treated patients (60.35%, OR=0.60, 95% CI 0.45 to 0.78, p<0.001). Review limitations included a high level of heterogeneity between studies analyzed.

Chapman (2015) conducted a retrospective analysis of outcomes of liver transplant compared to resection in 1765 HCC patients treated across five U.S. centers.[39] There were 884 patients who underwent resection and 881 who underwent transplantation. Of the resected patients, 248 (28.1%) were eligible for transplantation, according to the MILAN criteria; which were compared with 496 transplant patients, matched based on year of transplantation and tumor status. Five- and 10-year survival rates were significantly higher in transplant patients, compared to resected patients eligible for transplant (74% vs. 53% and 54% vs. 22% respectively, p<0.001). The investigators concluded that although transplantation results in better long-term survival, resection will likely remain a standard therapy in selected patients with HCC due to limited donor availability.

Zheng (2013) reported on a meta-analysis of 62 cohort studies (n=10,170 total patients) comparing liver transplantation to liver resection for HCC.[40] Overall one-year survival was similar between procedures (OR 1.08, 95% CI 0.81 to 1.43, p=0.61). However, overall three- and five-year survival significantly favored liver transplantation over resection (OR 1.47, 95% CI 1.18 to 1.84, p<0.001, and OR 1.77, 95% CI 1.45 to 2.16, p<0.001, respectively). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than liver resection patients at one, three, and five years, respectively (p<0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR 0.20, CI 0.15 to 0.28, p<0.001). While liver transplantation outcomes appear favorable compared to liver resection, a shortage of donor organs may necessitate liver resection as an alternative to liver transplantation.

Salvage Liver Transplantation after Liver Resection for Hepatocellular Carcinoma

In patients who have a recurrence of HCC after primary liver resection, salvage liver transplantation has been considered a treatment alternative to repeat hepatic resection, chemotherapy or other local therapies such as radiofrequency ablation, transarterial chemoembolization percutaneous ethanol ablation or cryoablation. Several systematic reviews have evaluated the evidence on outcomes of salvage transplant compared to primary transplant.

Yadav (2018) published a systematic review and meta-analysis comparing salvage liver transplant (SLT) and primary LT for individuals with hepatocellular carcinoma.[41] Twenty retrospective studies (10 of which were also included in Murali [2017], described below) with a total of 9,879 patients were included in the analysis. One-year overall survival was better for SLT (74.30%) than primary LT (OR 0.86, 95% CI 0.75 to 0.98, p=0.03). SLT also had higher three- (55.69% and 59.07%, respectively; OR 0.85, 95% CI 0.76 to 0.96, p=0.01) and five-year

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(48.67% and 52.32%, respectively; OR 0.85, 95% CI 0.76 to 0.96, p=0.009) overall survival than primary LT. One- (OR 0.86, 95% CI 0.75 to 0.99, p=0.03), three- (OR 0.56, 95% CI 0.39 to 0.81, p=0.002), and five-year DFS (OR 0.75, 95% CI 0.66 to 0.86, p<0.001) were worse for primary LT (70.03%, 74.08%, and 47.09%, respectively) than for SLT (67.69%, 57.02%, and 41.27%, respectively). There was no significant difference between the two groups for postoperative biliary complications (p=0.19) or sepsis (p=0.68). No limitations to the analysis were reported.

Murali (2017) published a systematic review and meta-analysis comparing primary LT to locoregional therapy with curative intent (CLRT) followed by SLT.[42] Forty-eight studies with 9,835 patients were included in the review, which found that five-year overall survival and disease-free survival were worse for the CLRT compared with primary LT (OR for overall survival 0.59, 95% CI 0.48 to 0.71, p<0.01), but there was no significant difference between primary LT and CLRT followed by SLT. However, only 32.5% of patients who had disease recurrence after CLRT received SLT, so disease-free survival was worse with CLRT-SLT.

A systematic review of 14 non-randomized comparative studies was published by Zhu (2013) (n=1,272 for primary transplant and n=236 for salvage).[43] Overall survival at one, three, and five years, and disease-free survival at one and three years were not significantly different between groups. Disease-free survival, however, was significantly lower at five years in SLT compared to primary transplantation (OR 0.62, 95% CI 0.42 to 0.92, p=0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria but in patients meeting Milan criteria, survival outcomes were not significantly different suggesting SLT may be a viable option in these patients.

Chan (2013) systematically reviewed 16 non-randomized studies (n=319) on SLT after primary hepatic resection for HCC.[44] The authors found overall and disease-free survival outcomes with SLT were similar to reported primary LT outcomes. The median overall survival for SLT patients was 89%, 80% and 62% at one, three, and five years, respectively. Disease-free survival was 86%, 68% and 67% at one, three, and five years, respectively. SLT studies had median overall survival rates of 62% (range 41 to 89%) compared to a range of 61% to 80% in the literature for primary LT. Median disease-free survival rates for SLT were 67% (range 29% to 100%) compared to a range of 58 to 89% for primary liver transplantation. Given a limited donor pool and increased surgical difficulty with salvage liver transplantation, further studies are needed. UNOS criteria indicate LT candidates with HCC who subsequently undergo tumor resection must be prospectively reviewed by a regional review board for the extension application.

In a meta-analysis, Li (2012) compared primary LT to SLT (liver transplantation after liver resection) for HCC.[45] Included in the meta-analysis were 11 case-controlled or cohort studies totaling 872 primary LTs and 141 SLTs. Survival rates of patients who exceeded the Milan criteria at one, three and five years were not significantly different between the two groups (one-year OR 0.26, 95% CI 0.01 to 4.94, p=0.37, three-year OR 0.41, 95% CI 0.01 to 24.54, p=0.67, and five-year OR 0.55, 95% CI 0.07 to 4.48, p=0.57).

Adenomatosis

Chiche (2016) published a prospective study that evaluated data from the European Liver Transplant Registry (ELTR) for 49 patients who had LT for liver adenomatosis (LA) between January 1, 1986 and July 15, 2013.[46] LA is a rare benign disease that does not affect liver function. It therefore does not increase the MELD score used to determine who should receive

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a transplant. The most prevalent concern is fear of malignant transformation and severe bleeding. The authors concluded LA is a rare indication for LT and can be handled non-surgically or through other surgical approaches. LT for LA carries an increased risk of morbidity/mortality, and criteria are critical to aid in transplant selection.

Cholangiocarcinoma

Reports on LT for cholangiocarcinoma (CCA), or bile duct carcinoma, generally distinguish between intrahepatic and extrahepatic tumors, the latter including hilar or perihilar tumors. Recent efforts have focused on pretransplant downstaging of disease with neoadjuvant radiochemotherapy. Relevant outcomes included waiting time duration; dropout rates, survival time, and recurrence.

Lunsford (2018) evaluated neoadjuvant chemotherapy followed by LT in a small, prospective case series of patients with locally advanced, unresectable, intrahepatic CCA at a single center.[47] Of the 21 patients referred between 2010 and 2017, 12 were accepted and six had undergone LT. Three of the transplants were from deceased donors and three were from living donors. All six patients survived to one year after transplant, and five patients survived to three and five years. Three had disease recurrence during follow-up.

Hildebrand (2016) published a multi-center retrospective cohort study to evaluate risk factors, recurrence of biliary strictures, and impact on survival after LT, for patients with primary sclerosing cholangitis (PSC).[48] PSC is a progressive cholestatic disease with inflammation and fibrotic strictures within the hepatic or extrahepatic bile ducts. Progression leads to biliary cirrhosis, recurrent episodes of septic cholangitis, or CCA. The only cure is LT. This study evaluated 2,170 transplant patients with prior PSC. LT was performed at 10 German transplant centers from January 1990 to December 2006. One-, five-, and 10-year recipient survival was 90.7%, 84.8%, and 79.4%, respectively, and one-, five-, and 10-year graft survival was 79.1%, 69.0%, 62.4%. Biliary strictures were found in 36.1% of the recipients after an average of 3.9 years, and recurrent PSC was found in 20.3% of the recipients after 4.6 years post-LT. MELD and Mayo risk score parameters, particularly INR, were higher in patients with biliary stricture after LT. Donor age was also a risk factor for developing strictures after LT.

Gu (2012) reported on a systematic review and meta-analysis of 14 clinical trials on LT for CCA.[49] Overall one-, three-, and five-year pooled survival rates from 605 study patients were 0.73 (95% CI 0.65 to 0.80), 0.42 (95% CI 0.33 to 0.51), and 0.39 (95% CI 0.28 to 0.51), respectively. When patients received adjuvant therapies preoperatively, one-, three-, and five-year pooled survival rates improved and were 0.83 (95% CI 0.57 to 0.98), 0.57 (95% CI 0.18 to 0.92), and 0.65 (95% CI 0.40 to 0.87), respectively.

Darwish Murad (2012) reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar CCA followed by LT.[50] Intent-to-treat survival (after a loss of 71 patients before liver transplantation) was 68% at two years and 53% at five years, and recurrence-free survival rates post-transplant were 78% at two years and 65% at five years. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria by having a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy. ($p<0.001$).

Panjala (2011) published results from a small case series of 22 patients with CCA treated with neoadjuvant chemoradiotherapy and subsequent LT.[51] Estimated rates of one, two, and three year survival, were 90%, 70%, and 63%, respectively, calculated based upon survival after a

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median follow-up of 601 days. Smaller tumors and those in the earliest stages of disease were associated with the most promising outcomes.

Among the various publications, the Mayo Clinic in Minnesota had the most favorable results.[52,53] Between 1993 and 2006, 65 patients underwent LT for unresectable perihilar CCA or had perihilar tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and five-year survival was 76%. In a series of 38 patients from the Mayo Clinic, cumulative recurrence was 0% at one year, 5% at three years, and 13% at five years.

The University of California, Los Angeles (UCLA)/Cedars-Sinai reported on 25 cases of both intrahepatic and extrahepatic CCA.[54] One-year survival was 71% and 3-year survival was 35%. The University of Pittsburgh found one-year survival of 70% and 18% five-year survival among 20 patients with intrahepatic CCA.[55] A German study of 24 patients reported the poorest results.[56]

The European Liver Transplant Registry reported that, among 186 patients with intrahepatic CCA, one-year survival was 58% and five-year survival was 29%.[57] In 169 patients with extrahepatic CCA, the probabilities were 63% and 29%. The Cincinnati Transplant Registry reported on 207 patients with either intrahepatic or extrahepatic CCA, finding a one-year survival of 72% and a five-year survival of 23%.[58] The multicenter report included 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.[59] One-year survival was 82% and 77%, while five-year survival was 30% and 23%, respectively. Crude recurrence rates were 53% and 36% for extrahepatic and intrahepatic CCA, respectively. The German center at Hannover found a crude recurrence rate of 63%.[56]

Table 2. Outcomes Among Patients with Cholangiocarcinoma

Study	Outcome	Group	n	Probability (%)			
				1yr	2yr	3yr	5yr
Pascher (2003)[31] European Liver Transplant Registry	Overall patient survival	IH-CCA	186	58		38	29
		EH-CCA	169	63		38	29
Meyer (2000)[32] Cincinnati Transplant Registry unresectable CCA, cholangiohepatoma, incidental median follow-up 23 mo (<1-96)	Overall patient survival	IH/EH-CCA	207	72	48		23
Robles (2004)[35] Multiple Centers in Spain 03/88-09/01; hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental	Overall patient survival	Hilar CCA	36	82		53	30
		Peripheral CCA	23	77		65	23
	Crude recurrence rate: EH-CCA: 19/36 (53%); IH-CCA: 8/23 (35%)						
Heimbach (2006)[52]; Rea (2006)[53] Mayo Clinic, Rochester MN, USA 01/93-01/06, aggressive neoadjuvant radiochemotherapy, unresectable perihilar CCA or perihilar CCA from primary sclerosing cholangitis mean follow-up 32 mo (2 d-13 yr)	Overall patient survival	Perihilar CCA	65	91			76
	Cumulative recurrence		38	0		5	13
	Crude recurrence rate: 11/65 (17%) median onset 22 mo (7-65)						
		All	25	71		35	

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Shimoda (2001)[54] UCLA/Cedars-Sinai, Los Angeles, CA, USA 1984-2000; IH or EH CCA median follow-up 22.3 mo	Overall patient survival	IH-CCA	16	62		39	
		EH-CCA	9	86		31	
	Disease-free survival	All	25	67		42	
		IH-CCA	16	70		35	
		EH-CCA	9	57		57	
Casavilla (1997)[55] University of Pittsburgh, PA, USA 1981-1994	Overall patient survival	IH-CCA	20	70		29	18
	Tumor-free survival		20	67		31	31
Weimann (2000)[56] Hannover, GER 07/78-12/96; unresectable CCA	Overall patient survival	IH-CCA	24	21	8	4	0
	Crude recurrence rate: 15/24 (63%)						
CCA: cholangiocarcinoma; EH: extrahepatic; IH: intrahepatic							

Heimbach (2018) reviewed the published outcomes of the combined protocol in the context of data on outcomes for surgical resection, and concluded that outcomes of neoadjuvant chemoradiotherapy with subsequent LT for patients with early-stage hilar CCA, which is unresectable, or arising in the setting of PSC are comparable to outcomes for patients with hepatocellular carcinoma and other chronic liver diseases, and superior to resection.[60] Intraoperative challenges attributable to the neoadjuvant therapy were described, including severe inflammatory changes and dense fibrosis. The author suggested that key principles for centers considering use of the combined protocol include a multidisciplinary approach, pretransplant staging, inclusion of only patients without lymph node metastasis, replacement of irradiated vessels (when possible), and monitoring for postoperative vascular complications.

Wu (2008) described an extensive surgical procedure combined with radiotherapy.[61] The authors retrospectively reviewed their experience with surveillance and early detection of CCA and en bloc total hepatectomy-pancreaticoduodenectomy-orthotopic liver transplantation (OLT-Whipple) in a small series of patients with early-stage CCA complicating PSC. Surveillance involved endoscopic ultrasound and endoscopic retrograde cholangiopancreatography and cytological evaluation. Patients diagnosed with CCA were treated with combined extra-beam radiotherapy, lesion-focused brachytherapy, and OLT-Whipple. CCA was detected in eight of the 42 patients followed up according the surveillance protocol between 1988 and 2001, and six patients underwent OLT-Whipple. One died at 55 months after transplant of an unrelated cause without tumor recurrence, and five are without recurrence at 5.7 to 10.1 years.

Section Summary

Treatment benefit of liver transplant has been demonstrated for select patients with CCA and evidence on patients with perihilar CCA have shown reasonable survival rates at five years. However, current evidence regarding five-year survival rates for intrahepatic CCA are less certain as most studies which demonstrated lower overall survival rates reported on a combined intra- and extra-hepatic patient population.

Pediatric Hepatoblastoma

Hepatoblastoma is a rare malignant primary solid tumor of the liver that occurs in children. Treatment consists of chemotherapy and resection; however, tumors aren't often discovered until they are unresectable. In cases of unresectable tumors, LT with pre- and/or post-chemotherapy is a treatment option with reports of good outcomes and high rates of survival.[62] UNOS guidelines list non-metastatic hepatoblastoma as a condition eligible for pediatric LT.[1]

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Hamilton (2017) reported on 376 children with hepatoblastoma requiring liver transplantation; this was part of a larger cohort of 544 children receiving a liver transplant from 1987 to 2012, as recorded in the United Network for Organ Sharing database.[63] The five-year patient survival rate after liver transplant for hepatoblastoma was 73%, with five-year graft survival rate of 74%. Recurrent or metastatic disease was the most common (57%) cause of death for this population.

Barrena (2011) reported on 15 children with hepatoblastoma requiring LT.[64] Overall survival after liver transplant was 93.3 (±6.4%) at one-, five- and 10-years. Malek (2010) reported on liver transplantation results for 27 patients with primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007.[65] Tumor recurrence occurred in one patient after LT and overall survival was 93%. Browne (2008) reported on 14 hepatoblastoma patients treated with LT. Mean follow-up was 46 months with overall survival in 10 of 14 patients (71%).[66] Tumor recurrence caused all four deaths. In the 10 patients receiving primary LT, nine survived while only one of four patients transplanted after primary resection survived (90% vs. 25%, p=0.02).

Metastatic Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are relatively rare neoplasms that are generally slow growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection. In select patients with non-resectable, hormonally active liver metastases refractory to medical therapy, LT has been considered as an option to extend survival and minimize endocrine symptoms.

Moris (2017) published a systematic review on LT for the treatment of NETs with liver metastases.[67] There were 64 studies deemed eligible for inclusion in the review, including four studies using registry data and three multicenter studies. The authors reported an overall recurrence rate ranging from 31.3% to 56.8%, with a five-year survival of 63%. Factors that were associated with worse survival included >50% liver tumor involvement, higher Ki67 (a disease marker) and pancreatic NETs (compared to gastrointestinal NETs).

Sher (2015) conducted a retrospective analysis on LT outcomes of 85 patients with NETs, assessing data from a North American multicenter database.[68] One, three, and five-year patient survival rates were 83%, 60%, and 52%, respectively. These rates are similar to those reported in larger studies. Overall, 40 of 85 patients died, with 20 of 40 deaths due to recurrent disease. In multivariable analysis, predictors of poor overall survival included large vessel invasion (p=0.001), and extent of extrahepatic resection at liver transplant (p=0.015). The investigators reported that the survival outcomes are high enough to merit LT in this patient population.

Fan (2014) reported on a systematic review of 46 studies on LT for NET liver metastases of any origin.[69] A total of 706 patients were included in the studies reviewed. Reported overall five-year survival rates ranged from 0 to 100%, while five-year disease-free survival rates ranged from 0% to 80%. In studies with more than 100 patients, the five-year overall survival rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after LT were reported in most studies.

Mathe (2011) conducted a systematic review of the literature to evaluate patient survival after LT for pancreatic NETs.[70] Data from 89 transplanted patients from 20 clinical studies were included in the review. Sixty-nine patients had primary endocrine pancreatic tumors, nine

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patients had carcinoids, and 11 patients were not further classified. Survival rates at one-, three-, and five-years were 71%, 55%, and 44%, respectively. The mean calculated survival rate was 54.45 (±6.31) months, and the median calculated survival rate was 41 months (95% CI 22 to 76 months).

Gedaly (2011) reported on a retrospective analysis of LT conducted on 150 patients with metastatic NETs.[71] Survival rates at one-, three-, and five-years were similar to those reported in the systematic analysis above: 81%, 65%, and 49%, respectively. No significant differences were seen in rates of patient survival between patients with metastatic NETs compared with those with hepatocellular carcinoma. Because longer wait times were associated with improved health outcomes, the authors suggested allowing for disease stabilization before attempting transplantation.

Mazzaferro (2007) performed a literature review to establish transplant selection criteria for patients with metastatic neuroendocrine tumors.[72] Eight studies were reviewed between 1970 and 2006, and all but one study reported either poor or limited five-year survival outcomes. Suboptimal patient selection was reported as the cause for the lower rates of long-term survival. However, the authors reported outcomes for 24 patients who were selected for transplant using the Milan criteria,[73] and found a high five-year survival rate of 77%. Although, the utilization of these criteria to select optimal transplantation candidates in patients with non-resectable metastatic neuroendocrine tumors is promising, the data is limited to a small sample (n=24), from a single study. Larger, long-term studies are required to validate the usefulness of the Milan criteria in improving five-year survival rates for this unique patient population.

Section Summary

While there may be centers that perform LT on select patients with NETs, further studies are needed to determine appropriate selection criteria. Few studies are available, and the quality is limited by their retrospective nature and heterogeneous populations.

HIV POSITIVE RECIPIENTS

The subgroup of HIV positive LT recipients was historically controversial due to the long-term prognosis for HIV positivity, and the impact of immunosuppression on HIV disease. HIV candidates for LT are frequently co-infected with HBV or HCV, and viral co-infection can further exacerbate drug-related hepatotoxicities.

Cooper (2011) conducted a systematic review to evaluate LT in patients co-infected with HIV and hepatitis.[74] The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI 81.1% to 87.8%) at 12 months. Patients were 2.89 (95% CI 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared to those with detectable HIV viremia.

Terrault (2012) reported on a prospective, multicenter study to compare LT outcomes in three groups: patients with both HCV and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older.[75] Patient and graft survival reductions were significantly associated with only one factor: HIV infection. At three years, patient and graft survival rates were significantly better in the HCV-only group (79%, 95% CI 72% to 84%, and 74%, 95% CI 66% to 79%, respectively) than in the group with both HIV and HCV infection (60%, 95% CI 47% to 71%, and 53%, 95% CI 40% to 64%, respectively).

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Current, OPTN policy permits HIV-positive transplant candidates.[1]

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney transplantation in patients with HIV disease.[76] These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- CD4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
- No opportunistic infections for at least six months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

Section Summary

While HIV infection reduced three-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival. Overall, survival rates are relatively high for patients with viral loads are low at the time of transplantation.

NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic steatohepatitis (NASH) is a condition where fat build up in the liver causes inflammation of the liver. LT is a treatment option for patients with NASH who progress to liver cirrhosis and failure.

In a systematic review and meta-analysis, Wang (2014) evaluated nine studies comparing LT outcomes in patients with and without NASH.[77] Patients with NASH had similar one-, three- and five-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had lower graft failure risk than those without NASH (OR 0.21, 95% CI 0.05 to 0.89, p=0.03). However, NASH LT patients had a greater risk of death related to cardiovascular disease (OR 1.65, 95% CI 1.01 to 2.70, p=0.05) and sepsis (OR 1.71, 95% CI 1.17 to 2.50, p=0.006) than non-NASH liver transplant patients. Given the relatively equivocal survival rates compared to transplant patients without NASH, transplant in patients with NASH appear to be of benefit.

Cholankeril (2017) published a retrospective cohort analysis of records from 2003 to 2014 in the United Network Organ Sharing and Organ Procurement and Transplantation Network database to evaluate the frequency of NASH-related liver transplantation.[78] In all, 63,061 patients underwent liver transplant from 2003 to 2014. NASH accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to NASH increased by 162.0%, a greater increase than either hepatitis C (33.0% increase) and alcoholic liver disease (55.0% increase). Five-year survival posttransplant in patients who had NASH (77.81%, 95% CI 76.37% to 79.25%) was higher than patients who had hepatitis C (72.15%, 95% CI 71.37 to 72.93, p<0.001). Patients with NASH also demonstrated significantly higher posttransplant survival than patients with hepatitis C (HR 0.75, 95% CI 0.71 to 0.79, p<0.001).

Section Summary

The evidence on LT for hepatocellular disease includes case series, registry studies, and systematic reviews. Long-term survival rates in patients with viral hepatitis are significant in a group of patients who have no other treatment options. Also, survival can be improved by

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eradication of hepatitis virus before transplantation. For patients with NASH, a 2013 systematic review has indicated that overall survival rates are similar to other indications for LT.

ELDERLY DONORS AND RECIPIENTS

Elderly Donors

Gao (2019) evaluated trends in long-term outcomes for LT with donors aged 60 years and above, using data from the OPTN/UNOS database.[79] There were 14,796 adult LT between 1990 and 2014 included in the analysis. There was a steady increase in the number of transplants from older donors found during the first 15 years of period, followed by a leveling off. There were significant improvements in the unadjusted five-year graft and patient survival over time ($p<0.0001$), as well as a reduction in the survival difference between older and younger grafts ($p<0.0001$).

A prospective study by Cascales-Campos (2018) assessed LT outcomes for those with donors aged 80 years and above (n=36) compared to those with donors under 65 years of age (n=283). They reported no significant differences in graft survival and overall survival.[80]

Paterno (2016) published a study that evaluated the outcome of LT from elderly donors.[81] Data from January 2007 to December 2011 was evaluated for patients who received a transplant from donors aged 70 years and older (n=540) or from patients younger than 60 years of age (n=10,473). The authors stated transplants from elderly donors in patients who meet criteria (i.e., no hepatitis C and not on dialysis) had good outcomes and survival rates, but slightly lower graft survival.

A similar study by Dasari (2017) with 4,376 LT recipients compared outcomes for those receiving grafts from deceased donors over 70 years of age (n=880) and below 70 years of age (n=3,496).[82] In this study, graft and patient survival were similar between groups at one year, but there was better graft and patient survival at three and five years in the older donor group.

Elderly Recipients

Chen (2016) published a population based cohort study that reported age-related LT mortality for patients in Taiwan.[83] Data were collected for patients receiving transplants from July 1, 1998 to December 31, 2012, and patients were followed until the end of the study or death. The authors stated the older a recipient, the higher risk of mortality, particularly for those with comorbidities.

Section Summary

Liver transplants for elderly recipients or from elderly donors can have positive health outcomes. More studies are needed to further identify survival rates and risks of mortality.

RETRANSPLANTATION

Agüero (2016) published an international cohort study that evaluated retransplantation for HIV patients who had hepatitis B (HBV) or HCV coinfection.[84] Thirty-seven patients with HBV or HCV coinfection underwent retransplant, with a survival rate of 80%. The authors concluded that patients coinfected with HBV or HCV, without HCV RNA had acceptable outcomes.

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Abdelfattah (2015) reported on a retrospective cohort of 466 LT patients, 16 of whom underwent retransplantation.[85] The 16 retransplant patients were divided into those which had retransplantation within 30 days of the primary transplant, and those which had retransplantation more than 30 days after. Although the investigators stated that, overall patient and graft survival were lower after liver retransplant than primary liver transplant, and these outcomes were better in late than early liver retransplant; the study populations in the comparator groups was too small to draw meaningful conclusions. Studies of larger sample size are needed.

Bellido (2012) reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data.[86] Survival probability using Kaplan-Meier curves with log-rank tests to compare 21 urgent versus 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%) related to chronic rejection.

Remiszewski (2011) examined factors influencing survival outcomes in 43 liver retransplantation patients.[87] When compared to primary LT patients, retransplantation patients had significantly lower six-year survival rates (80% vs. 58%, respectively, p=0.0001). The authors also reported low negative correlations between survival time and time from original transplantation until retransplantation and between survival time and patient age. Survival time and cold ischemia time showed a low positive correlation.

Hong (2011) reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation.[88] Eight risk factors were identified as predictive of graft failure, including age of recipient, MELD score greater than 27, more than one prior liver transplant, need for mechanical ventilation, serum albumin of less than 2.5 g/dL, donor age greater than 45 years, need for more than 30 units of packed red blood cells transfused intraoperatively, and time between prior transplantation and retransplantation between 15 and 180 days. The authors propose this risk-stratification model can be highly predictive of long-term outcomes after adult liver retransplantation and can be useful for patient selection.

Section Summary

Recent data regarding liver retransplantation suggest survival rates are not as good as with initial transplantation; however, overall survival rates appear to meet the benchmark of 50% five-year survival.

PRACTICE GUIDELINE SUMMARY

In December 2010, 10 international liver diseases or transplantation societies held an international consensus conference on liver transplantation for HCC.[89] Consensus criteria for selecting candidates for LT were developed at the conference. Milan criteria were recommended for use as the benchmark for patient selection and as the basis for comparison with other suggested criteria for selecting non-HCC patients. The Milan criteria set limits on the size and quantity of tumors and have been shown to be an independent prognostic factor for outcomes after LT.[89,90] Panel members did refer to several studies which indicated that in some circumstances, the Milan criteria may be modestly expanded for patients who do not have HCC. It was warned, however, that expanding Milan criteria could result in a variety of outcomes and that patients, "…would need to achieve 5-year survival of 60% or higher to prevent a substantial decrement to the life-years available to the entire population of

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candidates for liver transplantation."[89] In addition, candidates for LT should also have a predicted survival of five years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

With respect to liver retransplantation, the consensus criteria issued a weak recommendation indicating retransplantation after graft failure of a living donor transplant for HCC is acceptable in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued indicating liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria is not recommended. And the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC is not appropriate. However, a de-novo HCC may be treated as a new tumor and retransplantation may be considered even though data to support this are limited.

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)

Evaluation for Liver Transplantation

The AASLD issued separate updated, evidence-based guidelines for evaluating pediatric[91] and adult[92] patients for LT. These guidelines update the 2005 guidelines[93] which addressed all ages. While the disease categories are similar for adult and pediatric (below 18 years of age) patients, separate guidelines were considered warranted because of differences between these age groups in specific etiologies and outcomes. Furthermore, the AASLD guidelines indicate patients should be assessed by a transplantation center to determine whether LT is appropriate. While the AASLD guidelines indicate LT may be appropriate in patients with CCA and metastatic NETs, these recommendations and many of the recommendations in the AASLD guidelines are based on opinion.

- In 2014 the AASLD in conjunction with the American Society of Transplantation (AST) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition issued evidence-based guidelines for the evaluation of pediatric patients for liver transplantation.[91] Each of the 93 recommendations was classified for strength of recommendation and quality of evidence. Strength of recommendation 1 and 2 is defined as a strong or weak recommendation, respectively. Quality of evidence A, B, or C is defined as high, moderate, or low quality, respectively. Contact of or referral to a liver transplant center was recommended for any of the following indications:
    - Acute liver failure or acute decompensation of an established liver disease (*Strength of recommendation 1; quality of evidence A [1-A])*
    - Liver-based metabolic crises refractory to medical and/or surgical therapy *(1-B)*
    - Unresectable hepatoblastoma or hepatocellular carcinoma *(1-B)*
    - Biliary atresia patients with total bilirubin > 6 mg/dL beyond 3 months post-hepatoportoenterostomy (*1-B*); liver transplant evaluation should be considered in these patients if total bilirubin remains between 2-6 mg/dL. *(1-B)*
    - Anticipate referral for evaluation for children with chronic liver disease and evidence of deteriorating liver function (i.e., poor weight gain, growth failure, variceal hemorrhage, intractable ascites, recurrent cholangitis, or episodes of spontaneous bacterial peritonitis, pruritus, advancing encephalopathy, and/or uncorrectable coagulopathy *(1-B)*

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- The 2013 AASLD/ATS guideline for evaluation of adults for LT state that LT is indicated for acute or chronic liver failure when the limits of medical therapy have been reached.[92] The following are some of the included recommendations:
    - Consideration for liver transplantation is recommended for acute liver failure complications of cirrhosis, liver-based metabolic conditions with systemic manifestations, and systemic complications of chronic liver disease (i.e., hepatopulmonary syndrome; portopulmonary hypertension)
    - Liver transplant in combination with neoadjuvant chemoradiation for early-stage unresectable peri-hilar cholangiocarcinoma *(1-B)*.
    - Intrahepatic cholangiocarcinoma is a listed contraindication to liver transplant
    - Extrahepatic malignancy is a contraindication to liver transplant
    - Live donor transplant should be considered only when a deceased donor is unlikely to become available within a reasonable time frame for the recipient's liver disease

Long-term Management after Liver Transplant

The AASLD has also issued joint evidence-based guidelines with the AST for management of pediatric[94] and adult[95] patients following successful LT. Numerous recommendations are included and each is graded for strength of recommendation and quality of the supporting evidence. The stated intent of the guidelines is to provide flexible, preferred approaches to the diagnostic, therapeutic, and preventive aspects of care.

The 2013 guideline for pediatric (age 0 to 18 years) post-LT patients includes 54 recommendations.[94] "Pediatric liver transplant has dramatically changed the prognosis for many infants and children with liver failure and metabolic disease. As survival increases, long-term maintenance resources exceed perioperative care requirements. The most common indication for LT in children is biliary atresia which accounts for 50% of all children requiring transplant in the U.S. and 74% in Europe."

The 2012 AASLD/AST practice guideline for adults after LT includes 93 recommendations.[95] "LT is the treatment of choice for patients with decompensated cirrhosis, acute liver failure, small hepatocellular carcinomas (HCCs), or acute liver failure…long-term survivors are at risk of early death and increased morbidity. The purpose of this guideline is to assist in the management of adult recipients of LT, identify the barriers to maintaining their health, and make recommendations on the ways to best prevent or ameliorate these barriers. This guideline focuses on management beyond the first 90 days after transplantation."

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The NCCN guidelines on hepatobiliary cancers (v1.2020) made the following level 2A recommendations based on lower-level evidence and uniform consensus:[37]

- Patients with potentially resectable or transplantable, operable by performance status or comorbidity can undergo surgical assessment.
- Patients with unresectable disease should be evaluated for transplant candidacy using UNOS criteria.
- For patients meeting UNOS criteria, refer to liver transplant center and consider bridge therapy as indicated. In addition, there are several footnotes relevant to the recommendation including but not limited to the following:

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- Patients with Child-Pugh Class A liver function, who meet UNOS criteria and are resectable could be considered for resection or transplant.
- There are patients whose tumor characteristics are marginally outside of the UNOS guidelines who should be considered for transplant. Furthermore, there are patients who are downstaged to within criteria that can also be considered for transplantation.

The NCCN guidelines on neuroendocrine and adrenal tumors (v1.2019) indicate that liver transplantation for neuroendocrine tumor metastases in the liver is considered investigational and not part of routine care at this time.[96]

SUMMARY

There is enough research to show that liver transplantation can improve survival for patients with irreversible, end-stage liver failure due to certain conditions. Clinical guidelines based on research recommend liver transplantation for some people with irreversible, end-stage liver failure. Therefore, liver transplantation may be considered medically necessary in patients who meet the policy criteria.

There is enough research to show that liver transplantation does not improve health outcomes for patients with hepatocellular carcinoma that has extended beyond the liver, or for patients with active alcohol and/or substance abuse. Therefore, liver transplantation is considered not medically necessary for these patients.

There is not enough research to show that liver transplantation improves survival for patients with intrahepatic cholangiocarcinoma, extrahepatic malignancy other than those noted in the policy criteria, or neuroendocrine tumors metastatic to the liver. Therefore, liver transplantation is investigational for these populations when the policy criteria are not met.

RETRANSPLANTATION

There is enough research to show that liver retransplantation improves survival for pediatric and adult patients for primary graft nonfunction, hepatic artery thrombosis, chronic rejection, ischemic type biliary lesions after donation after cardiac death, or recurrent non-neoplastic disease-causing late graft failure. Therefore, liver retransplantation may be considered medically necessary in patients with one of these diagnoses who meet the policy criteria. There is not enough research to show that liver retransplantation improves survival in patients for other conditions. Therefore, liver retransplantation is investigational when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	47133	Donor hepatectomy (including cold preservation) from cadaver donor
	47135	Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
	47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into two partial liver grafts (i.e., left lateral segment (segments II and III) and right trisegment (segments I and IV through VIII))
	47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into two partial liver grafts (i.e., left lobe (segment II, III, and IV) and right lobe (segments I and V through VIII)
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	47399	Unlisted procedure, liver
HCPCS	None	

Date of Origin: *January 1996*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 06

Pancreas Transplant

Effective: December 1, 2019

Next Review: August 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation of a normal pancreas is a treatment method for patients with diabetes.

MEDICAL POLICY CRITERIA

Note: Islet cell transplantation is considered in a separate medical policy (see Cross References).

I. Pancreas transplant may be considered **medically necessary** when both of the following (A. and B.) are met:
   A. Candidates must meet both of the following general criteria:
      1. Adequate cardiopulmonary status; and
      2. Documentation of patient compliance with medical management.
   B. Transplant for any of the following indications:
      1. A combined pancreas-kidney transplant in diabetic patients with uremia; or
      2. Pancreas transplant after a prior kidney transplant in patients with insulin-dependent diabetes mellitus (IDDM); or

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3. Pancreas transplant alone in patients with documentation of any of the following conditions, which persist despite optimal medical management:
    a. Severely disabling and potentially life-threatening hypoglycemia unawareness as evidenced by chart notes or emergency room visits; or
    b. Potentially life-threatening labile diabetes as evidenced by documentation of erratic blood glucose levels and hemoglobin A1c equal to or greater than 8% or hospitalization for diabetic ketoacidosis.

II. Pancreas retransplantation may be considered **medically necessary** after one failed primary pancreas transplant.

III. Pancreas transplantation that does not meet criterion I. or II. is considered **not medically necessary.**

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

MULTIPLE TRANSPLANTS

Although there are no standard guidelines regarding multiple pancreas transplants, the following information may aid in case review:

- If there is early graft loss resulting from technical factors (e.g., venous thrombosis), a retransplant may generally be performed without substantial additional risk.
- Long-term graft losses may result from chronic rejection, which is associated with increased risk of infection following long-term immunosuppression, and sensitization, which increases the difficulty of finding a negative cross-match. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- Pre-transplant evaluation including pulmonary status and pertinent co-morbidities and treatments
- Failed primary pancreas transplant

CROSS REFERENCES

1. Islet Cell Transplantation, Transplant, Policy No. 13

BACKGROUND

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Pancreas transplantation can restore glucose control, and is intended to prevent, halt, or reverse the secondary complications of insulin dependent Type 1 diabetes mellitus (IDDM). Achievement of insulin independence with resultant decreased morbidity and increased quality of life is the primary health outcome of pancreas transplantation. While pancreas transplantation is generally not considered a life-saving treatment, in a small subset of patients who experience life-threatening complications from IDDM, pancreas transplantation could be considered life-saving. In addition to the immune rejection issues common to all allograft transplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes.[1]

Pancreas transplantation occurs in several different scenarios such as:

1. Type 1 diabetic patient with renal failure who may receive a cadaveric simultaneous pancreas/kidney transplant (SPK)
2. Type 1 diabetic patient who may receive a cadaveric or living-related pancreas transplant after a kidney transplantation (pancreas after kidney, i.e., PAK)
3. Non-uremic type 1 diabetic patient with specific severely disabling and potentially life-threatening diabetic problems who may receive a pancreas transplant alone (PTA).

PTA has also been investigated in patients following total pancreatectomy for chronic pancreatitis. The experience with SPK transplants is more extensive than that of other transplant options.

The approach to retransplantation varies according to the cause of failure. Surgical/technical complications such as venous thrombosis are the leading cause of pancreatic graft loss among diabetic patients. Graft loss from chronic rejection may result in sensitization, increasing both the difficulty of finding a cross-matched donor and the risk of rejection of a subsequent transplant. Each center has its own guidelines based on experience; some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

EVIDENCE SUMMARY

SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANT

The U.S.-based Organ Procurement and Transplant Network (OPTN) reported a one-year patient survival rate of 97.5% (95% confidence interval [CI] 96.9% to 98.0%) for SPK procedures performed between 2008 and 2015.[2] Three- and five-year patient survival rates were 94.7% (95% CI 93.9% to 95.5%) and 88.6% (95% CI 87.5% to 89.7%), respectively.

Barlow (2017) analyzed U.K. registry data that compared outcomes in patients with type 1 diabetes and end-stage renal disease who had SPK transplants (n=1739) with live donor kidney transplants (n=370).[3] In multivariate analysis, there was not a significant association between type of transplant and patient survival (HR [hazard ratio] 0.71, 95% CI 0.47 to 1.06; p=0.095). SPK recipients with a functioning pancreas graft had significantly better overall survival than those with a living donor kidney transplant (p<0.001).

According to international registry data through 2005, five-year graft survival rates for simultaneous pancreas/kidney (SPK) transplants were 72% for the pancreas and 80% for the kidney.[4] Ten-year graft survival rates reached almost 60% for SPK transplants. The U.S.-

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based OPTN reported a five-year survival rate of 85.5% (95% CI 84.3% to 86.7%) for SPK procedures performed between 1997 and 2000.[5]

Pancreas transplant has been found to improve mortality in patients with type 1 diabetes. Van Dellen (2014) reported a retrospective analysis of data on 148 SPK patients and a wait-list control group of 120 patients.[6] The study also included 33 patients who had PAK and 11 PTA patients. All patients had uncomplicated type 1 (insulin dependent) diabetes. Overall mortality was 30% (30/120 patients) on the waiting list and patients who underwent transplantation had a mortality rate of 9% (20/193 patients); the difference between groups was statistically significant ($p<0.001$). One-year mortality was 13% (n=16) on the waiting list and 4% (n=8) in the transplant group ($p<0.001$).

There are some data on outcomes in patients with type 2 compared with type 1 diabetes. Sampaio (2011) published an analysis of data from the United Network for Organ Sharing (UNOS) database.[7] The investigators compared outcomes in 6,141 patients with type 1 diabetes and 582 patients with type 2 diabetes who underwent SPK between 2000 and 2007. In adjusted analyses, outcomes were similar in the two groups. After adjusting for other factors such as body weight; dialysis time; and cardiovascular comorbidities, type 2 diabetes was not associated with an increased risk of pancreas or kidney graft survival or mortality compared to type 1 diabetes.

Mora (2010) described the long-term outcome of 12 patients 15 years following SPK transplant.[8] Metabolic measures of glucose control were measured at 1, 5, 10, and 15 years following the procedure. Of this subset of patients, six (50%) had non-diabetic glucose challenge tests. Basal serum insulin levels declined over this period as well, from 24 mU/L to 16 mU/L at 1 and 15 years, respectively. The authors concluded that in a select group of patients whose pancreatic graft continued to function after 15 years, some glycemic control continued, albeit in a diminished fashion. It should be noted that this represented a small fraction of the 367 patients receiving the SPK transplant at this single center (12 of 367 SPK; 3.3%). The number of allograft survivals at five or more, and 10 or more years in this study was 43 (11.7%) and 28 (7.6%), respectively.

The improved glycemic control that may occur in SPK transplant patients, principally in those with labile disease while on medical therapy alone, is purported to reduce risk of complications from the diabetic disease. Davenport (2009) published results of a registry review (n=58) on cardiovascular risk factors in an Irish study of SPK transplant recipients.[9] Glycosylated hemoglobin values fell from a mean of 8.1 to 5.2 ($p<0.0001$) from pre-transplant levels. Similar statistically significant declines were seen in total cholesterol, triglycerides, and creatinine. Systolic and diastolic blood pressures were likewise improved but with a greater range of pre- and post-transplant variability. These endpoints are commonly accepted as surrogates for cardiovascular risk. The authors compared both a surgical method (bladder vs. enteric drainage) and mode of immunosuppression (cyclosporine vs. tacrolimus) on changes to blood pressure and cholesterol. No significant differences were found in either measure based on surgical drainage method, nor did immunosuppressive therapy have an impact on blood pressure reduction. Cholesterol reduction was greater in the cyclosporine than the tacrolimus group (-1.3 to -0.2, respectively), favoring the less contemporary strategy. The authors noted that this was in contrast to other recently published studies favoring both enteric drainage and tacrolimus. While this single arm study suggested beneficial cardiovascular effects from transplant, other factors such as rejection rates were more likely to influence the conditions under which transplantations took place.

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PANCREAS AFTER KIDNEY TRANSPLANT[10]

Gruessner and Gruessner (2016) reported updated patient survival rates for pancreas after kidney (PAK) transplants. According to UNOS and International Registry data, patient survival after PAK from 2010 to 2014 was 97.9% after one year and 94.5% after three years.[11] This compares with one-year and three-year patient survival rates for 2005 to 2009 of 96.4% and 93.1%, respectively.

PAK transplantation allows the uremic patient the benefits of a living-related kidney graft, if available, and the benefits of a subsequent pancreas transplant that is likely to result in improved quality of life compared to a kidney transplant alone. Uremic patients for whom a cadaveric kidney graft is available but a pancreas graft is not simultaneously available benefit similarly from a later pancreas transplant. Based on international pancreas registry data, at five years post-transplant, the patient survival rate after PAK is 83%.[12]

Bazerbachi (2012) reviewed a single center's experience with PAK and synchronous pancreas-kidney (SPK) transplantations.[13] Between 2002 and 2010, 172 pancreas transplants were performed in diabetic patients; 123 SPK and 49 PAK. The median length of time between kidney and pancreas transplantation in the PAK group was 4.8 years. Graft and patient survival rates were similar in the two groups. Death-censored pancreas graft survival rates for SPK and PAK were 94% and 90% at one year, 92% and 90% at three years, and 85% and 85% at five years (all respectively, p=0.93). Patient survival rates (calculated beginning at the time of pancreas transplantation) in the SPK versus PAK groups were 98.3% and 100% after one year, 96.4% and 100% after three years, and 94.2% and 100% after five years (all respectively, p=0.09).

Fridell (2009) reported a retrospective review (n=203) of a single center's experience with PAK and SPK since 2003, when current induction/tacrolimus immunosuppressive strategies became standard.[14] Of the cases studied, 61 (30%) were PAK and 142 (70%) were SPK. One-year patient survival rates were 98% and 95% (PAK and SPK, respectively; p=0.44). Pancreas graft survival rates at one year were observed to be 95% and 90%, respectively (p=0.28). The authors conclude that in the modern immunosuppressive era, PAK should be considered as an acceptable alternative to SPK in candidates with an available living kidney donor.

Kleinclauss (2009) retrospectively examined data from diabetic kidney transplant recipients (n=307) from a single center and compared renal graft survival rates in those who subsequently received a pancreatic transplant to those who did not.[15] The comparative group was analyzed separately depending on whether they were medically eligible (KTA-E) for pancreas transplant, but chose not to proceed for financial or personal reasons, or were ineligible (KTA-I) for medical reasons. The KTA-I (n=57) group differed significantly at baseline from both the PAK group (n=175) and the KTA-E group (n=75) with respect to age, type of diabetes and dialysis experience; kidney graft survival rates were lower than either of the other groups, with 1-, 5-, and 10-year rates of 75%, 54%, and 22%, respectively (p<0.0001). The PAK and KTA-E groups were similar in age, race, type of diabetes, and dialysis experience. The authors compared 1-, 5-, and 10-year kidney graft survival rates in PAK patients with those in the KTA-E group: 98%, 82%, and 67% versus 100%, 84%, and 62%, respectively, and concluded that the subsequent transplant of a pancreas after a living donor kidney transplant did not adversely affect patient or kidney graft survival rates.

PANCREAS TRANSPLANT ALONE[10]

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Gruessner and Gruessner (2016) reported updated patient survival rates for PTA.[11] According to UNOS and the International Registry data, for the period of 2010 to 2014, patient survival after PTA was 96.3% after one year and 94.9% after three years. This compares with one-year and three-year patient survival rates of 97.5% and 93.3% for 2005 to 2009, respectively.

According to international registry data one-year graft function increased from 51.5% in 1987-1993 to 77.8% in 2006-2010 ($p<0.0001$).[12] One-year immunologic graft loss remains higher (6%) after PTA than PAK (3.7%) or SPK (1.8%). In carefully selected IDDM patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile diabetes that persists despite optimal medical management, the benefits of PTA were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression. The majority of patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where non-uremic IDDM patients have significant morbidity risks due to secondary complications of diabetes (e.g., peripheral neuropathy) that exceed those of the transplant surgery and subsequent chronic immunosuppression. Because there is virtually no published evidence regarding outcomes of medical management in this very small group of exceptional diabetic patients, it is not possible to generalize about which circumstances represent appropriate indications for pancreas transplantation alone. Case-by-case consideration of each patient's clinical situation may be the best option for determining the balance of risks and benefits.

Noting that nephrotoxic immunosuppression may exacerbate diabetic renal injury after PTA, Scalea (2008) reported a single institutional review of 123 patients who received 131 PTA for development of renal failure.[16] Mean graft survival was 3.3 years (range, 0 to 11.3), and 21 patients were lost to follow-up. Mean estimated glomerular filtration rate (eGFR) was 88.9 pre-transplantation versus 55.6 post-transplantation, with mean follow-up of 3.7 years. All but 16 patients had a decrease in eGFR, and mean decrement was 32.1 mg/min/1.73. Thirteen developed end-stage renal disease, which required kidney transplantation at a mean of 4.4 years. The authors suggested that patients should be made aware of the risk and only the most appropriate patients offered PTA. Future updates of this policy will continue to follow this clinical topic.

PANCREAS RETRANSPLANTATION[17]

Several centers have published outcomes after pancreas retransplantation.

Rudolph (2015) reported higher graft survival rates, but not patient survival rates, after primary transplant.[18] A total of 2145 pancreas transplants were performed, 415 (19%) of which were retransplants. Death-censored graft survival at one year was 88.2% in initial transplants and 75% in retransplants ($p=0.06$).

Fridell (2015) reported on 441 initial transplants and 20 late transplants.[19] One-year graft survival rates were 92% after initial transplant and 90% after retransplant ($p=0.48$). Similarly, one-year patient survival rates were 96% after initial transplants and 95% after retransplants ($p=0.53$).

Siskind (2015) published the largest comparative study to date which included long-term outcomes for 1149 retransplant patients and 19,705 primary transplant patients.[20] Patient data was collected from the UNOS database (1996-2012) and PAK, PTA, PWK and SPK patients were included in the analysis. Adjusted patient survival rates were compared at 1-, 3-, 5-, 10-,

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and 15-year follow-up. Analysis of 30-day retransplantation outcomes was not performed due to small sample size. Graft survival was significantly worse in the retransplant group compared to primary transplant at all follow-up points, for all transplant types:

Table 1: Graft Survival

Graft Survival	Primary Transplant, %	Retransplant, %	P
1 year	85.44	37.16	<0.0001
3 year	76.86	21.93	<0.0001
5 year	69.23	14.45	<0.0001
10 year	52.26	2.79	<0.0001
15 year	36.96	0.17	<0.0001

Table 2: Patient Survival

Patient Survival	Primary Transplant, %	Retransplant, %	P
1 year	94.83	98.99	<0.0001
3 year	90.20	96.67	<0.0001
5 year	85.41	93.19	<0.0001
10 year	71.85	79.80	<0.0001
15 year	58.86	54.93	<0.0001

Authors speculated that the improved survival rates in the retransplantation group could be attributed to retransplantation of the kidney with the pancreas versus pancreas alone; however, subgroup analysis did not support this hypothesis. These study findings significantly differ from previous nonrandomized comparative studies which have indicated pancreas retransplantation has comparable graft survival rates to primary transplant.

According to data posted by the OPTN, for the period 1997-2004, patient survival rates were similar for primary transplants and repeat transplants.[5] For example, the one-year survival rate among 1,216 individuals who had a primary pancreas transplant was 94.0% (95% CI 92.6 to 95.3%), and the one-year survival rate among 256 patients with a repeat pancreas transplant was 95.6% (95% CI 92.7 to 98.5%). Three-year survival rates were 89.5 (95% CI: 87.8 to 91.2%) for 1,004 patients with primary transplants and 89.7% (95% CI 85.9% to 93.5%) for 225 patients with repeat transplants. One-year graft survival rates were 78.2% (95% CI 76.0 to 80.5%) after primary pancreas transplants and 70.4% (95% CI 64.8 to 76.0%) after repeat transplants.

Data were similar for patients receiving combined kidney/pancreas transplants, but follow-up data were only available on a small number of patients who had repeat kidney/pancreas transplants, so estimates of survival rates in this group were imprecise. Three-year patient survival rates were 90% (95% CI 89.0 to 91.0%) for 2,902 patients who had a primary transplant and 79.9% (95% CI 63.8 to 95.9%) for 26 patients who had a repeat transplant.

Seal (2014) reported on 96 consecutive PTA patients treated at a single center in Canada; 78 were initial transplants, and 18 were retransplants.[21] Pancreas graft survival was similar for primary transplants and retransplants at one year (88% vs 100%, p=0.88) and three years (85% in both groups, p=0.99). Patient survival rates were also similar in the two groups at one year (96% and 100%, p=0.95) and three years (93% and 100%, p=0.93).

Buron (2013) reported on their experience with pancreas retransplantation in France and Geneva.[22] Between 1976 and 2008, 568 pancreas transplants were performed at two centers, including 37 repeat transplants. Patient survival after a repeat pancreas transplant was 100%

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after one year and 89% after five years. Graft survival was 64% at one year and 46% at five years. Among the 17 patients who underwent a second transplant in a later time period i.e., between 1995 and 2007, graft survival was 71% at one year and 59% at five years. In this more recently transplanted group, graft survival rates were similar to primary pancreas transplants which was 79% at one year and 69% at five years.

Studies for pancreatic retransplantation are limited to retrospective reviews and non-randomized feasibility studies. The evidence for graft and patient survival following the first retransplantation of the pancreas following PAK, PTA, or SPK transplantation has shown outcomes similar to primary transplantation.[5,18,23-26] No clinical trials were found that reported survival outcomes following more than one retransplantation.

HIV+ TRANSPLANT RECIPIENTS

The Organ Procurement Transfer Network (OPTN) permits HIV test positive patients as organ candidates if permitted by the transplant hospital.[27]

In 2009, the Clinical Practice Committee of the American Society of Transplantation and the American Society of Transplant Surgeons proposed that the presence of AIDS could be considered a contraindication to kidney transplant unless the following criteria were present.[28] These criteria may be extrapolated to other organs:

- CD4 count >200 cells/mm-3 for ≥6 months
- HIV-1 RNA (i.e., viral load) undetectable ≥ 3 months
- On stable anti-retroviral therapy ≥3 months
- No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioses mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
- Meeting all other criteria for transplantation

A retrospective analysis of all deceased donor pancreas transplants performed in the U.S. between 1988 and 1999 revealed that since the mid-1990's allograft half-lives ranged from eight to nine years for PTA transplants to nearly 13 years for SPK transplants.[29] The data indicates that insulin-independence with functioning grafts can been achieved for longer than 20 years.

AGE

In the past 5 to 10 years, several analyses of outcomes by patient age group have been published and there is now general agreement among experts that age should not be a contraindication; however, age-related comorbidities are important to consider when selecting patients for transplantation.

Siskind (2014) used data from the United Network for Organ Sharing (UNOS) database to publish the largest study of pancreas outcomes by recipient age.[30] Investigators included all adult patients who received SPK or PTA between 1996 and 2012 (n=20,854). There were 3160 patients between the ages of 50 and 59 years, and 280 patients age 60 or older. Overall, Kaplan-Meier survival analysis found statistically significant differences in patient survival ($p<0.001$) and graft survival ($p<0.001$) among age categories. Graft survival was lowest in the 18- to-29 age group at 1, 5, and 10 years, which the authors noted might be due to early immunological graft rejection due to more robust immune responses. However, 10 and 15 year

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graft survival was lowest in the 60 and older age group. Patient survival rates decreased with increasing age, and the differential between survival in older and younger ages increased with longer follow-up intervals. Lower survival rates in patients 50 and older could be due in part to comorbidities at the time of transplantation. Also, as patient age, they are more likely to die from other causes. Still, patient survival at 5 and 10 years was relatively high, as shown in Table 3.

Table 3: Patient Survival by Age Group[30]

	Age 18-29, %	Age 30-39, %	Age 40-49, %	Age 50-59, %	Age 60+, %
1 year	95.4	96.0	94.9	93.3	91.0
5 years	86.3	87.8	85.7	81.6	71.4
10 years	73.5	76.8	71.8	61.5	42.5

Shah (2013) reviewed data on 405 patients who underwent PTA between 2003 and 2011.[31] One-year patient survival was 100% for patients younger than age 30, 98% for patients age 30 to 39 years, 94% for patients 40 to 49 years, 95% for patients 50 to 59 years and 93% for patients age 60 or older. There was not a statistically significant difference in the rate of patient survival by age (p=0.38). Findings were similar for 1-year graft survival; there was not a statistically significant difference in outcomes by age of the transplant recipients (p=0.10).

In addition, several 2011 studies addressed pancreas transplantation in individuals 50 years of age or older. Afaneh (2011) reviewed data on 17 individuals at least 50-years-old and 119 individuals younger than 50 who had a pancreas transplant at a single institution in the U.S.[32] The two groups had similar rates of surgical complications, acute rejection and non-surgical infections. Overall patient survival was similar. Three- and five-year survival rates were 93% and 90% in the younger group and 92% and 82% in the older group.

Schenker (2011) in Germany compared outcomes in 69 individuals at least 50-years-old and 329 individuals younger than 50 years who had received a pancreas transplant.[33] Mean duration of follow-up was 7.7 years. One-, five-, and 10-year patient and graft survival rates were similar in the two groups. For example, the five-year patient survival rate was 89% in both groups. The five-year pancreas grant survival rate was 76% in the older group and 72% in the younger group. The authors of both studies, as well as the authors of a commentary accompanying the Schenker article,[34] agreed that individuals age 50 years and older are suitable candidates for pancreas transplantation.

PRACTICE GUIDELINE SUMMARY

AMERICAN DIABETES ASSOCIATION

The American Diabetes Association (ADA) Position Statement made the following recommendations on kidney and pancreas transplantation for patients with type 1 diabetes:[35]

- "Consider solid organ pancreas transplantation simultaneously with kidney transplantation in patients with type 1 diabetes who have an indication for kidney transplantation and are poorly controlled with large glycemic excursions. (B)"
- "Consider solid organ pancreas transplantation after kidney transplantation in adult patients with type 1 diabetes who have already received a kidney transplant. (C)"
- "Judiciously consider solid organ pancreas transplantation alone in adults with type 1 diabetes, unstable glucose control, hypoglycemia unawareness, and an increased risk of diabetes-related mortality, who have attempted all of the more traditional approaches to

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glycemic control and have remained unsuccessful, yet are judged responsible enough to manage the antirejection medication regimen, risks, and follow-up required with an organ transplant. (C)"

ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK

The Board of Directors of the Organ Procurement and Transplantation Network (OPTN) issues an updated comprehensive list of transplant related policies regularly, most recently in June 2018.[36]

Each candidate registered on the pancreas waiting list must meet *one* of the following requirements:

- Be diagnosed with diabetes
- Have pancreatic exocrine insufficiency
- Require the procurement or transplantation of a pancreas as part of a multiple organ transplant for technical reasons

Each candidate registered on the kidney-pancreas waiting list must meet *one* of the following requirements:

- Be diagnosed with diabetes
- Have pancreatic exocrine insufficiency, with renal insufficiency

In addition, waiting time criteria indicated that for kidney-pancreas transplant candidates 18 years and older, candidates must meet *all* of the following conditions:

1. The candidate is registered for a kidney-pancreas.
2. The candidate qualifies for kidney waiting time according to *Policy 8.4: Waiting Time*.
3. The candidate meets *at least one* of the following criteria:
    a. Is on insulin and C-peptide less than or equal to 2 ng/mL
    b. Is on insulin and C-peptide greater than 2 ng/mL and has a body mass index (BMI) less than or equal to the maximum allowable BMI.

The OPTN policy also delineated pancreas, kidney-pancreas, and islet allocation, classifications, and rankings.

SUMMARY

SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION (SPK)

There is enough research to show that simultaneous pancreas kidney (SPK) improves outcomes (e.g. normalizes insulin production and kidney function, improves quality of life, and improves diabetic complications) for diabetic patients. Therefore, SPK transplantation for diabetic patients may be medically necessary when policy criteria are met.

PANCREAS AFTER KIDNEY TRANSPLANT (PAK)

There is enough research to show that pancreas after kidney transplant (PAK) improves health outcomes for diabetic patients. The International Pancreas Transplant Registry provides information that PAK improves health outcomes in some diabetic patients who have

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previously received a successful kidney transplant. Therefore, PAK transplantation for diabetic patients may be considered medically necessary when policy criteria are met.

PANCREAS TRANSPLANT ALONE (PTA)

There is enough research to show that pancreas transplantation improves health outcomes including quality of life and reduce short complications for people with diabetes. Therefore, pancreas transplantation for diabetic patients that have conditions which persist after optimal medical management may be considered medically necessary when policy criteria are met.

RETRANSPLANTATION

There is enough research to show that the health outcomes for pancreas retransplantation recipients appear similar to those reported for initial transplants. Therefore, retransplantation after one failed primary pancreas transplant may be considered medically necessary when policy criteria are met.

There is not enough research to show that a third or subsequent pancreas transplant improves health outcomes and there are documented safety concerns. Therefore, a third or subsequent pancreas transplant including simultaneous kidney-pancreas transplant, pancreas after kidney transplant, or pancreas alone transplant are considered not medically necessary when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels,

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		and Y-graft arterial anastomosis from the iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
HCPCS	S2065	Simultaneous pancreas kidney transplantation
	S2152	Solid organs(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

Date of Origin: *January 1996*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 08

Lung and Lobar Lung Transplant

Effective: June 1, 2020

Next Review: March 2021
Last Review: April 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

A lung transplant consists of replacing all or part of diseased lungs with healthy lung(s). Transplantation is an option for patients with end-stage lung disease.

MEDICAL POLICY CRITERIA

I. Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy.

II. A lobar lung transplant from a living or deceased donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease.

III. Lung or lobar lung retransplantation after a failed lung or lobar lung transplant may be considered **medically necessary** in patients who meet either criterion I or II.

IV. Lung or lobar lung transplantation is considered **not medically necessary** in all other situations.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

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POLICY GUIDELINES

End-stage pulmonary disease may include, but is not limited to, the following diagnoses:

- Alpha-1 antitrypsin deficiency
- Bilateral bronchiectasis
- Bronchiolitis obliterans
- Bronchopulmonary dysplasia
- Chronic obstructive pulmonary disease
- Cystic fibrosis (both lungs to be transplanted)
- Eisenmenger's syndrome
- Emphysema
- Eosinophilic granuloma
- Idiopathic/interstitial pulmonary fibrosis
- Lymphangiomyomatosis
- Postinflammatory pulmonary fibrosis
- Primary pulmonary hypertension
- Pulmonary hypertension due to cardiac disease
- Recurrent pulmonary embolism
- Sarcoidosis
- Scleroderma

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Heart/Lung Transplant, Transplant, Policy No. 3

BACKGROUND

End-stage lung disease may be the consequence of a number of different conditions. The most common indications for lung transplantation are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. Prior to the consideration for transplant, patients should be receiving maximal medical therapy, including oxygen supplementation, or surgical options, such as lung-volume reduction surgery for COPD. Lung or lobar lung transplantation is an option for patients with end-stage lung disease despite these measures.

A lung transplant refers to single-lung or double-lung replacement. In a single-lung transplant, only one lung from a deceased donor is provided to the recipient. In a double-lung transplant, both the recipient's lungs are removed and replaced by the donor's lungs. In a lobar transplant, a lobe of the donor's lung is excised, sized appropriately for the recipient's thoracic dimensions, and transplanted. Donors for lobar transplant have primarily been living-related

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donors, with one lobe obtained from each of two donors (e.g., mother and father) in cases for which bilateral transplantation is required. There are also cases of cadaver lobe transplants. Combined lung-pancreatic islet cell transplant is being studied for patients with cystic fibrosis.[1]

Since 2005, potential recipients have been ranked according to the Lung Allocation Score (LAS).[2] Patients 12 years of age and older receive a score between 1 and 100 based on predicted survival after transplantation reduced by predicted survival on the waiting list; the LAS takes into consideration the patient's disease and clinical parameters. In 2010, a simple priority system was implemented for children younger than age 12 years. Under this system, children younger than 12 with respiratory lung failure and/or pulmonary hypertension who meet criteria are considered "priority 1" and all other candidates in the age group are considered "priority 2." A lung review board has the authority to adjust scores on appeal for adults and children.

EVIDENCE SUMMARY

Due to the nature of the population, there are no randomized controlled trials (RCTs) that compare lung transplantation with alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, or immunosuppressive therapy and are not germane to this policy. Therefore, the following is a summary of the evidence based on registries, case series, and expert opinion.

SURVIVAL

The Registry of the International Society for Heart and Lung Transplantation (ISHLT) contains data from 49,453 adult recipients who received lung transplantation (including lung retransplantation) through June 30, 2015, at 134 transplant centers.[3] A total of 55,795 lung transplants were performed, of which 53,522 (95.9%) were primary transplants and 2,273 (4.1%) were retransplants. The overall median survival of patients who underwent lung transplantation was 5.8 years. Estimated unadjusted survival rates were 89% at three months, 80% at one year, 65% at five years, and 32% at 10 years. Patients who survived a year after primary transplantation had a median survival of 8.0 years. In the first 30 days after transplantation, the major reported causes of mortality were graft failure (24.5%) and non-cytomegalovirus (CMV) infections (19.1%), while non-CMV infections became the major cause of death for the remainder of the first year. Beyond the first year, the most common reported causes of mortality were obstructive bronchiolitis/bronchiolitis obliterans syndrome (OB/BOS), graft failure, and non-CMV infections. Beyond 10 years post-transplant, the major causes of mortality were OB/BOS (21.5%), non-CMV infection (16.5%) and non-lymphoma malignancy (13.7%).

The ISHLT registry contains a total of 2,229 pediatric lung transplants performed through 2014.[4] Most transplants (73%) were done in older children between the ages of 11 to 17 years. Median survival in children who underwent lung transplantation was 5.4 years, similar to survival in adults (mean survival, 5.7 years). However, median survival in children was lower (2.2 years) than in adults (5.6 years) for single-lung transplants.

Black (2014) published results from an analysis of lung transplants using data from the United Network for Organ Sharing's (UNOS) Scientific Registry of Transplant Recipients from 1994 to June 2012.[5] The goal of the analysis was to evaluate how survival was affected in patients who had a high lung allocation score (LAS) and received a single versus a double lung

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transplant. In all, there were 8,778 patients identified; however, just 8,050 had a LAS less than 75, and 728 has a LAS greater than or equal to 75. Kaplan-Meier survival curves stratified by high and low LAS, and by single versus double lung transplants, showed a significant decrease in survival (p<0.001) in those with a high LAS who received a single lung transplant when compared with those with a high LAS who received a double lung transplant. The authors, that despite a higher operative morbidity, patients who had a high LAS did substantially better in terms of survival if two lungs were transplanted rather than only one, with a larger difference in survival than for patients with a lower LAS.

Thabut (2009) reported on a comparison of patients undergoing single- and double-lung transplantation for idiopathic pulmonary fibrosis.[6] A retrospective review was conducted of 3,327 patients with data in the UNOS registry. More patients underwent single-lung as compared to double-lung transplant (64.5 vs. 35.5%, respectively). Median survival time was greater for the double-lung group at 5.2 years (95% confidence interval [CI] 4.3 to 6.7 years) versus 3.8 years (95% CI 3.6 to 4.1 years, p<0.001). After adjustment for baseline differences, however, survival times were not statistically different. The authors concluded that overall survival did not differ between the two groups: single-lung transplants offered improved short-term survival but long-term harm, whereas double-lung transplant increased short-term harm but was associated with a long-term survival benefit. Later, Black (2014) reported on the LAS and single- versus double-lung transplant in 8,778 patients (8,050 had an LAS less than 75 and 728 had an LAS of 75 or higher).[5] A significant decrease in survival was seen in single-lung transplant patients with a high LAS compared with double-lung transplant patients with a high LAS, even though operative morbidity was higher (p<0.001).

Hayanga (2016) analyzed lung transplantation data from the UNOS registry between 2005 and 2013.[7] Survival was analyzed in relation to the annual volume of lung transplants performed at each center: less than 20, 20-29, 30-39, and 40 or more. During the study period, 13,506 adults underwent lung transplantation. Approximately 40% of the transplants were performed in centers with a volume of 40 or more, with the remaining transplants spread relatively equally across lower volume center groups. Both one- and five-year patient survival tended to increase with increasing volume, but the authors noted that it was a relatively small effect.

Kistler (2014) reported on a systematic review of the literature on waitlist and posttransplant survival for idiopathic pulmonary fibrosis.[8] Estimated median survival of idiopathic pulmonary fibrosis patients posttransplantation is estimated at 4.5 years and is lower than other underlying pretransplant diagnoses. From ISHLT and the Organ Procurement and Transplantation Network (OPTN) data, one-year survival ranged from 75% to 81%; three-year, 59% to 64%, and five-year, 47% to 53%. Limited data were available on posttransplant morbidity outcomes.

Taimeh (2016) reported on post-lung transplant survival in 695 patients with pulmonary sarcoidosis in the U.S.[9] Survival in this group was similar to that of non-sarcoid lung recipients, and in a multivariate analysis, sarcoidosis was not associated with higher mortality. In the sarcoidosis group, LAS and double lung transplantation were both associated with improved survival.

PATIENT SELECTION

Based on concern that the LAS may prioritize lung transplant candidates with a poor expected survival benefit from the procedure, Li (2019) analyzed data from the UNOS registry

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(n=21,157) to determine whether there was a LAS threshold above which the score did not predict increasing survival benefit.[10] The results of this analysis indicated that the greatest benefit was seen for recipients with scores between 70 and 79 (n=365), with a hazard ratio of death after undergoing transplantation relative to remaining on the waitlist of 0.2 (95% CI 0.1 to 0.3). Survival for patients with LAS scores above this range was not significantly increased. The authors noted that the survival benefit threshold for patients with cystic fibrosis was quite a bit lower, at a score of approximately 50.

Shafii (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation, and 426 who underwent primary lung transplantation between 2005 and 2010.[11] Patients on the waitlist who had a higher LAS had a higher rate of mortality (p<0.001). In the highest quartile of LAS, ranging from 47 to 95, within one year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival (p=0.05) but not late posttransplant survival (p=0.4). When other predictive factors of early mortality were accounted for, pretransplant LAS was not independently related to posttransplant mortality (p=0.12).

Russo (2011) analyzed a dataset of 6,082 patients who received a lung transplant between May 4, 2005 and May 4, 2009 in order to describe outcomes and estimate the survival benefit based upon patient lung allocation score.[12] Authors found that although lower priority patients comprise the majority of transplants, mid-priority groups with LAS of 50 to 79, seemed to achieve the greatest survival benefit from transplantation (2.81 to 3.49 years). Patients with the highest and lowest LAS score achieved the least survival benefit; however, it was noted that patients with high allocation scores were expected to have worse survival and that patients with lower LAS had the lowest risk of death on the waiting list. Data suggested that transplant centers may be justified in considering patients for lung transplantation who had a mid-range allocation scores before patients with the highest and lowest scores.

Yusen (2010) reviewed the effect of the LAS on lung transplantation by comparing statistics for the period before and after its implementation in 2005.[13] Other independent changes in clinical practice, which may affect outcomes over the same period of time, include variation in immunosuppressive regimens, an increased supply of donor lungs, changes in diagnostic mix, and increased consideration of older recipients. Deaths on the waiting list declined following implementation of the LAS system, from approximately 500 per 5,000 patients to 300 per 5,000 patients. However, it is expected that implementation of the LAS affected patient characteristics of transplant applicants. One-year survival post-transplantation did not improve after implementation of the LAS system: patient survival data before and after are approximately 83%. More recently, Shafii (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation and 426 who underwent primary lung transplantation between 2005 and 2010.[11] Patients on the waitlist who had a higher LAS had a higher rate of mortality (p<0.001). In the highest quartile of LAS, ranging from 47 to 95, within one year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival (p=0.05) but not late posttransplant survival (p=0.4). When other predictive factors of early mortality were accounted for, pretransplant LAS was not independently related to posttransplant mortality (p=0.12).

Gries (2010) published results from a study on pre-transplant characteristics of 10,128 patients from the Organ Procurement and Transplantation Network (OPTN) database were examined to understand how well LAS post-transplant survival model parameters predict one- and five-year survival.[14] Authors concluded that the LAS system and pre-transplant

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characteristics in general did not predict long term one- or five-year survival better than chance.

Kozower (2008) performed a retrospective cohort study using data from five academic medical centers to evaluate the impact of the LAS on short-term outcomes after lung transplantation.[15] (The LAS was implemented in May 2005 by the OPTN.) This score changed lung allocation from a system based on waiting time to an algorithm based on the probability of survival for one year on the transplant list and survival one-year post-transplantation. Results were compared for 170 patients who received transplants based on the new lung allocation scores (May 4, 2005 to May 3, 2006) with those of 171 patients who underwent transplants the preceding year before implementation of the scoring system. Waiting time decreased from 681 to 445.6 days (p<0.001). Recipient diagnoses changed, with an increase (15% to 25%) in idiopathic pulmonary fibrosis cases and decreases in emphysema (46% to 34%) and cystic fibrosis (23% to 13%). Hospital mortality and one-year survival were the same between groups (5.3% vs. 5.3% and 90% vs. 89%, respectively). Presumably due to increased severity of illness, the incidence of primary graft dysfunction and postoperative intensive care unit length of stay increased in the year after implementation of the scoring system; graft dysfunction grew from 14.8% (24/170) to 22.9% (39/171); (p=0.04) and length of stay rose from 5.7 to 7.8 days.

PEDIATRIC CONSIDERATIONS

Paraskeva (2018) analyzed survival rates of adolescent lung transplant recipients using data from the ISHLT registry.[16] Patients between 10 and 24 years old represented 9% of the registry data (n=2,319) and they were compared with both old and young cohorts. Overall survival in the adolescent cohort was 65% at three years, which was similar to that observed in adults between 50 and 65 years of age, but significantly lower than three-year survival rate among the pediatric subgroup (73%, p=0.006) or adults 25 to 34 years old (75%, p<0.001) and 35 to 49 years old (71%, p<0.001). Within the adolescent group, patients between 15 and 19 years of age had the poorest survival rates at three years (59%) compared with 10- to 14-year year old patients (73%) and 20- to 24-year old year patients (66%) (both p<0.001). The registry study was biased toward inclusion of North American data and potential data entry errors or missing data. There were no data reported on cause of mortality, differences in regimens, or rates of graft dysfunction between the groups.

Benden (2012) reviewed pediatric lung transplants that have been reported to the international registry.[17] Pediatric patients are defined as those younger than 18 years of age. The authors noted an increase in the number of pediatric lung transplants in recent years; there were 126 transplants in 2010 compared to 73 in 2000. In contrast to adult patients, the most common indication for pediatric patients was cystic fibrosis, accounting for 54% of lung transplants in 6- to 11-year-olds and 72% of lung transplants in 12- to17-year-olds that occurred between 1990 and June 2011. Survival has improved in the recent era, and five-year survival is not significantly different from adult recipients. The half-life, estimated time at which 50% of recipients have died, was 4.7 years for children and 5.3 years for adults. For children receiving allografts between 2002 and June 2010, the five-year survival rate was 54% and seven-year survival was 44%. Patients aged 1 to 11 years had a significantly better survival rate than those between the ages of 12 and 17 years (half-life of 6.2 years and 4.3 years, respectively). In the first year after lung transplantation, non-CMV infection and graft failure were the two leading causes of death. Bronchiolitis obliterans syndrome was the major cause of death beyond three years after transplantation.

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Moreno (2016) compared survival and clinical outcomes in pediatric and adult lung transplantation for cystic fibrosis at a single institution.[18] There were 120 patients included in the study: 50 children and 70 adults, who underwent 111 bilateral, four lobar, four combined and one unilateral lung transplant. Overall survival for children at five, ten, and 15 years was 57, 45, and 35% vs, 67, 55, and 43% for adults, respectively (p=0.32). Pediatric patients were significantly more likely than adults to have used cardiopulmonary bypass (56% vs. 28%, p=0.002), have acute rejection episodes (1.4 ± 0.7 vs. 1.2 ± 0.8, p=0.004), and stay longer in intensive care (20 ± 19 vs. 10 ± 9 days, p=0.006). The authors noted that pediatric cystic fibrosis patients presenting for lung transplant tend to have a worse status than adult patients, which might explain some of these differences.

Mangiameli (2016) reported on outcomes of pediatric lung transplantation at a center in France, with a focus on sex matching of donors and recipients.[19] In this study, which included 58 patients below age 18, the 30-day mortality was 10% and survival at one, five, and 10 years was 81%, 60%, and 57%, respectively. Among these patients, female sex and sex mismatching were associate with poor prognosis, with female recipients of male-donated organs having particularly poor outcomes.

A study by Fraser (2019) used information from the UNOS database to examine the role of size mismatch in preadolescent lung transplantation.[20] There were 540 patients included in the analysis, which found that one-year mortality was higher for patients with height and weight mismatching, and for predictive total lung capacity ratios less than 0.9 (p=0.017)

POTENTIAL CONTRAINDICATIONS

Malignancy

Concerns regarding a potential recipient's history of cancer have been based on the observation of significantly increased incidence of cancer in kidney transplant patients.[21] For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.[22,23] However, it should be noted that the availability of alternative treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage lung disease patients may not have an option to defer.

A 2012 study reported on outcomes in patients with lung cancer who were lung transplant recipients.[24] Ahmad and colleagues identified 29 individuals in the UNOS database who underwent lung transplantation for advanced bronchoalveolar carcinoma (BAC). These patients represented 0.13% of the 21,553 lung transplantations during the study period. BAC and general lung transplant recipients had similar survival rates: the 30-day mortality rate was 7% versus 10% (p=0.44) and five-year survival rate was 50% versus 57% (p=0.66), respectively.

HIV

Solid organ transplant for patients who are human immunodeficiency virus (HIV)-positive was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. The availability of highly active antiretroviral therapy (HAART) has markedly changed the natural history of the disease. However, there is little

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data directly comparing outcomes for patients with lung and lobar lung transplants with and without HIV.

As of October 2013, the Organ Procurement Transplantation Network (OPTN) policy on HIV status in recipients states: “A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy.”[25]

Other Infections

Infection with *Burkholderia cenocepacia* is associated with increased mortality in some transplant centers, a factor that may be considered when evaluating overall risk for transplant survival.[26]

A 2016 analysis of international registry data found that non-CMV infection is a major cause of mortality within 30 days of lung transplant in adults.[3] A total of 655 (19%) of 3,424 deaths after transplants between January 1990 and June 2015 were due to non-CMV infection. Only three (0.1%) of the deaths were due to CMV infection.

Wojarski (2018) assessed the impact of bacterial infection on mortality in 97 lung transplant patients from a single center between 2004 and 2016.[27] The mean hospitalization time was 57 days and 67 patients had a total of 120 episodes of bacterial infection. The most common sources of infection were *Pseudomonas aeruginosa* (27%), followed by *Acinetobacter baumannii* (21%), and *Stenotrophomonas maltophilia* (11%). There were 39 patients who developed bronchiolitis obliterans syndrome. *A. baumannii* infection was associated with decreased survival, while treatment with mammalian target of rapamycin inhibitors was linked to increased survival.

Lobo (2013) reported on 13 lung transplant patients with *Mycobacterium abscessus* in cystic fibrosis.[28] Survival rates were 77%, 64% and 50% after transplant at one, three, and five years, respectively. These results were not significantly different when compared to 154 cystic fibrosis patients treated with lung transplantation who did not have *M. abscessus* (p=0.8).

Shields (2012) reported on infections in 596 consecutive lung transplant recipients treated at a single center occurring in the first 90 days after transplantation.[29] A total of 109 patients (18%) developed 138 *Staphylococcus aureus* (*S. aureus*) infections. The most common type of infection was pneumonia (66 of 138, 48%) followed by tracheobronchitis (36 of 138, 26%) and bacteremia (17 of 138, 12%). Thirteen of 109 (12%) of patients with *S. aureus* infection died within 90 days of the onset of infection. The one-year mortality rate was higher for patients with *S. aureus* pneumonia (19 of 66, 29%) but not *S. aureus* tracheobronchitis (8 of 36, 22%) compared with uninfected patients (85 of 487, 17%).

Pinney (2011) published results from a retrospective review of invasive fungal infection rates in lung transplantation patients without cystic fibrosis treated at a single center.[30] Patients were followed for a median of 34 months. Invasive fungal infections were identified in 22 of 242 (9.1%) patients. *Aspergillus* infections were most common, occurring in 11 of 242 (4.5%) of patients. There were also seven cases (3%) of *Candida* infection. Survival rates did not differ significantly in patients with invasive fungal infections compared to the entire cohort of patients. For example, three-year survival was 50% among patients with invasive fungal infection and 66% in the entire cohort (p=0.66). The authors did not compare survival in

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patients with invasive fungal infections to survival only in those without invasive fungal infections.

In a study published by Murray (2008), multivariate Cox survival models assessing hazard ratios (HRs) were applied to 1,026 lung transplant candidates and 528 transplant recipients.[31] Of the transplant recipients, 88 were infected with *Burkholderia*. Among transplant recipients infected with *Burkholderia cenocepacia,* only those infected with nonepidemic strains (n=11) had significantly greater post-transplant mortality than uninfected patients (HR 2.52, 95% CI 1.04 to 6.12, p=0.04). Transplant recipients infected with *Burkholderia gladioli* (n=14) also had significantly greater post-transplant mortality than uninfected patients (HR 2.23, 95% CI 1.05 to 4.74, p=0.04). When adjustments for specific species/strains were included, lung allocation scores of *Burkholderia multivorans*-infected transplant candidates were comparable to uninfected candidate scores, and scores for patients infected with non-epidemic *B. cenocepacia* or *B. gladioli* were lower. In a smaller study of 22 patients colonized with *Burkholderia cepacia* complex who underwent lung transplantation in two French centers, the risk of death by univariate analysis was significantly higher for the eight patients infected with *B. cenocepacia* than for the other 14 colonized patients (11 of whom had *B. multivorans*).[32]

Coronary Artery Disease (CAD)

Castleberry (2013) reported on a retrospective cohort study of lung transplantation with concurrent CAB or preoperative percutaneous coronary intervention (PCI).[33] Out of 898 lung transplants performed during the period between 1997 and 2010, 49 patients also had concurrent CAB and 38 patients had preoperative PCI. All of the intervention groups, including revascularization, had similar rates of perioperative mortality, overall unadjusted survival and adjusted HR for cumulative risk of death. Postoperative major adverse cardiac event rates were also similar among groups, although postoperative length of stay, intensive care unit time and need for ventilator support increased in patients receiving concurrent CAB with lung transplantation.

Sherman (2011) reported on outcomes in 27 patients with CAD at a single center who underwent lung transplantation and coronary revascularization.[34] Patients needed to be otherwise considered good candidates for transplantation and have discrete coronary lesions (at least 50% in the left main artery or at least 70% in other major vessels) and preserved ejection fraction. Thirteen patients had single-lung transplantation and 14 had double-lung transplantation. Outcomes were compared with a control group of 81 patients without CAD who underwent lung transplantation; patients were matched for age, diagnosis, lung allocation score and type of procedure. During a mean follow-up of three years, nine of 27 (33%) patients with CAD and 28 of 81 (35%) without CAD died (p=0.91). Bronchiolitis obliterans and infection were the primary causes of death. There was no significant difference between groups in a composite outcome of adverse cardiac events (defined as acute coronary syndrome, redo revascularization or hospital admissions for congestive heart failure), p=0.80.

LOBAR LUNG TRANSPLANTATION

Several case series have reported outcomes after lobar lung transplants in both children and adults.

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Eberlein (2017) published a systematic review of studies on lobar lung transplantation from deceased donors.[35] Reviewers identified nine studies comparing outcomes after lobar lung or lung transplant, all of which were single-center retrospective cohort studies. Seven studies were conducted in Europe, one in Australia, and one in North America. One-year survival reported in individual studies ranged from 50% to 100% after lobar lung transplant and from 72% to 88% after conventional lung transplant. In a pooled analysis of data from eight studies, lobar lung transplant recipients (n=284) had a significantly higher risk of one-year mortality than lung transplant recipients (n=2,777) (relative risk [RR] 1.85, 95% CI 1.52 to 2.25, $p<0.001$, $I^2=0\%$).

Date (2014) reported on a retrospective study comparing 42 living-donor lobar lung transplants and 37 cadaveric lung transplants.[36] Survival rates at one and three years were not significantly different between the groups (89.7 and 86.1% vs 88.3 and 83.1%, respectively, p=0.55), despite living-donor lobar lung transplant patients having poorer health status preoperatively.

Slama (2014) reported on a comparison of outcomes in 138 cadaveric lobar lung transplants (for size discrepancies) to 778 patients who received cadaveric whole-lung transplants, 239 of whom had downsizing by wedge resection of the right middle lobe and/or the left lingula.[37] Survival in the lobar lung transplant group at one and five years was 65.1% and 54.9% versus 84.8% and 65.1% in the whole lung and downsized by wedge resection group ($p<0.001$). The lobar lung transplantation group experienced significantly inferior early postoperative outcomes, but in patients who were successfully discharged, survival rates were similar to standard lung transplantation (p=0.168).

In 2012, a program in Japan reported on 14 critically ill patients who had undergone single living-donor lobar lung transplants; there were ten children and four adults.[38] Patients were followed for a mean 45 months. The three-year survival rate was 70% and the five-year survival was 56%. Severe graft dysfunction occurred in four patients. Mean forced vital capacity (FVC) was found to be lower in patients experiencing severe graft dysfunction compared to the other patients, mean FVC was 54.5% and 66.5%, respectively. The authors stated that this suggests size mismatching in the patients with severe graft dysfunction. The same year, Inci (2012) published data on 23 patients in Switzerland who received bilateral lobar lung transplants.[39] The mean age was 41 years (range 13 to 66 years). Survival at one and two years was 82% and 64%, respectively; survival rates were comparable with 219 patients who underwent bilateral lung transplantation during the same period (p=0.56).

A review article by Date (2015) stated that, as of 2011, approximately 400 living-donor lobar lung transplants have been performed worldwide.[36] Procedures in the U.S. decreased after 2005 due to changes in the lung allocation system. The author stated that size matching between donor and recipient is important and that, to some extent, size mismatching (oversized or undersized grafts) can be overcome by adjusting surgical technique.

Several studies reported on lobar lung transplantation from living donors. For example, Barr (2005) reported on experience performing living donor lobar lung transplants in the U.S.[40] Ninety patients were adults and 43 were children. The primary indication for transplantation (86%) was cystic fibrosis. At the time of transplantation, 67% of patients were hospitalized and 20% were ventilator dependent. Overall recipient actuarial survival at one, three and five years was 70%, 54% and 45%, respectively. There was not a statistically significant difference in actuarial survival between adults and children who underwent transplantation.

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Moreover, survival rates were similar to the general population of lung transplant recipients. The authors also reported that rates of postoperative pulmonary function in patients surviving more than three months post-transplant were comparable to rates in cadaveric lung transplant recipients.

RETRANSPLANTATION

Registry data and case series reports have demonstrated favorable outcomes with lung retransplantation in certain populations, such as in patients who meet criteria for initial lung transplantation.[41-44]

OPTN reported data on lung transplants performed between 2008 and 2015.[45] Patient survival rates after repeat transplants were lower than primary transplants, but a substantial number of patients survived. For example, one-year patient survival was 87.9% (95% CI 87.2% to 88.7%) after a primary lung transplant and 76% (95% CI 70.9% to 80.2%) after a repeat transplant. Five-year patient survival was 55.9% (54.7% to 57.2%) after a primary lung transplant and 33.8% (28.5 to 39.1%) after repeat transplant.

The ISHLT registry contains data on 2,273 retransplantations performed through June 2015 (4.4% of all lung transplantations during this period).[3] The major causes of death in the first 30 days after retransplantation were graft failure and non-CMV infection, followed by multiorgan failure, cardiovascular causes and technical factors related to the transplant procedure. Beyond the first year, the most common reported causes of mortality were OB/BOS, graft failure, and non-CMV infections.

Biswas Roy (2018) published a single-center retrospective study comparing survival outcomes in 29 patients who received retransplantation for chronic lung allograft dysfunction with 390 patients receiving primary lung transplant at the same center.[46] Patients receiving retransplantation had significantly higher use of extracorporeal membrane oxygenation support for severe primary graft dysfunction (p=0.019) and underwent cardiopulmonary bypass and re-exploration for bleeding (p=0.019) more frequently than patients receiving primary transplantation (p=0.029). At one-year follow-up, 89.7% of primary transplant patients were living, as were 89.2% of retransplantation patients. At five-year follow-up, a greater percentage of the retransplantation group had survived, compared with the primary transplantation group (64.3% vs 58.2%), although the difference was not statistically significant. While high LAS and extended hospital length of stay were both identified as independent mortality risk factors, retransplantation was not (HR 1.58, 95% CI 0.31 to 8.08, p=0.58). Study limitations included its single-center, retrospective design, the potential selection bias for younger patients, and the small size of the retransplantation group. Further, follow-up data at three and five years were incomplete for some patients, and patients who were refused retransplantation were not considered in the analyses. However, for appropriately selected patients, retransplantation after chronic lung allograft dysfunction resulted in one- and five-year survival rates comparable to those seen after primary lung transplantation.

Thomas (2015) published results from a retrospective study that compared patient survival after lung retransplantation (LRTx) to primary lung transplantation (LPTx) in the U.S. using data from the UNO registry between 2004 and 2013.[47] A total of 582 LRTx and 13,673 LPTx recipients were included in the analysis. The median survival after LRTx was 2.6 years compared with 5.6 years after LPTx. One-year, three-year, and five-year survival rates were, respectively, 71.1%, 46.3%, and 34.5% for LRTx, and 84.3%, 66.5%, and 53.3% for LPTx (p<0.001). On multivariate analysis, patients who had LRTx after a greater than one-year

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interval survived longer (RR 0.53, 95% CI 0.34% to 0.88%, p=0.008). Lower survival was associated with single-lung transplantations (RR 1.49, 95% CI 1.06% to 2.07%, p=0.021), transplantations done between 2009 and 2013 (RR 1.40, 95% CI 1.01% to 1.94%, p=0.041), multiple retransplantations (RR 2.55, 95% CI 1.14% to 5.72%, p=0.023), and recipients requiring pre-transplantation ventilator support.

Kilic (2013) evaluated data on 390 adult lung retransplantation patients from the UNOS database.[42] Patients received lung retransplantation during the period May 2005 to December 2010, which was after the LAS selection criteria were implemented. Patients with reduced functional status were found to have poorer outcomes than patients with better functional status prior to retransplantation. Using the Karnofsky scale to stratify patients into functional status groups, the authors found the overall one-year survival of 56% for patients requiring total assistance before retransplantation was significantly lower than the overall one-year survival of 82% for patients who only required some assistance before retransplantation (p<0.001). The one-year mortality rate after risk adjustment was also increased significantly for patients requiring total assistance prior to retransplantation (odds ratio 3.72, p=0.02). While additional patient selection criteria may be useful for lung retransplantation, current LAS criteria are now used.

PRACTICE GUIDELINE SUMMARY

INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2015, the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation (ISHLT) published an update to their 2006 consensus-based guidelines on selection of lung transplant candidates.[48,49] The guidelines state:

> "… there is general agreement that referral to a lung transplant program should occur early in patients who have a lung disease that is amenable to transplantation. None of the parameters listed in this document informing on the timing of referral or listing should be used in isolation. Instead, the entire clinical situation of the patient should be considered. However, early referral does give the transplant program maximal flexibility in performing the formal evaluation and in making the second more important step—placing the patient on the active waiting list. Listing a patient for a lung transplant is an explicit acknowledgement that a patient has a limited life expectancy without a transplant and an expectation that the risk-to-benefit ratio favors lung transplantation rather than conventional medical treatment."

For lung retransplantation, the guidelines state:

> "Lung retransplantation accounts for a small percentage of lung transplants performed annually. However, its frequency has increased in recent years. The criteria for candidate selection for lung retransplantation generally mirror the criteria used for selection for initial lung transplantation. Survival after lung retransplantation may have improved over time but remains inferior to survival seen after initial transplantation. For the individual patient, retransplantation should be analyzed as a time-dependent survival risk factor. Consideration must also be given to ethical issues surrounding lung allocation to retransplantation candidates."

AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY/JAPANESE RESPIRATORY SOCIETY/LATIN AMERICAN THORACIC ASSOCIATION

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Evidence-based recommendations from the American Thoracic Society and three international respiratory/thoracic societies were published in 2011.[50] For appropriately selected patients with idiopathic pulmonary fibrosis, the group recommended lung transplantation (strong recommendation, low-quality evidence)

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

In 2017 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee members performed a literature search and developed guidelines regarding the diagnosis, management and prevention of chronic obstructive pulmonary disease.[51] The committee suggested that in carefully selected patients with COPD, lung transplantation has been shown to improve quality of life and functional capacity. The guidelines state:

> "In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered. … Criteria for referral for lung transplantation include COPD with progressive disease, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, Pco_2 greater than 50 mm Hg or 6.6 kPa and/or Pao_2 less than 60 mm Hg or 8 kPa, and FEV_1 less than 25% predicted."

These recommendations were made on the basis of evidence collected from observational studies; however, randomized controlled trials are unlikely in this patient population.

SUMMARY

There is enough research to show that lung transplantation can improve survival in certain patients and thus may be considered medically necessary for patients when the policy criteria are met. It may be the only option for some patients with end-stage lung disease.

There is enough research to show that lung retransplantation can improve survival and may be the only option for patients with failed lung transplantation. Therefore, lung retransplantation may be considered medically necessary in selected patients who meet criteria for lung transplantation.

Lung or lobar lung transplantation or retransplantation is considered not medically necessary in all other situations when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	32850	Donor pneumonectomy(ies) (including cold preservation), from cadaver donor
	32851	Lung transplant, single; without cardiopulmonary bypass
		;with cardiopulmonary bypass
	32853	Lung transplant, double (bilateral, sequential, or en bloc); without cardiopulmonary bypass
	32854	;with cardiopulmonary bypass
	32855	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus, unilateral
	32856	;bilateral
HCPCS	S2060	Lobar lung transplantation
	S2061	Donor lobectomy (lung) for transplantation, living donor

Date of Origin: *March 2013*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 09

Isolated Small Bowel Transplant

Effective: April 1, 2020

Next Review: January 2021
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Small bowel transplants are performed to treat intestinal failure in patients that require total parenteral nutrition (TPN) and are having serious TPN complications.

Note: A small bowel transplant may be performed in conjunction with other visceral organs, including the liver, duodenum, jejunum, ileum, pancreas, or colon. When the small bowel and liver are transplanted in conjunction with other gastrointestinal organs, the procedure is referred to as a multivisceral transplant. Small bowel/liver transplants and multivisceral transplants are considered separately (see cross-reference list below).

MEDICAL POLICY CRITERIA

I. Candidates for all types of small bowel transplant must meet all of the following criteria:
   A. Adequate cardiopulmonary status; and
   B. Documentation of patient compliance with medical management

II. Cadaveric Donor

A small bowel transplant using a cadaveric intestine may be considered **medically necessary** in adult and pediatric patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or

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micronutrient balance), who have established long-term dependency on total parenteral nutrition (TPN) and are developing or have developed one or more of the following severe complications due to TPN:

A. TPN intolerance to the point that multiple and prolonged hospitalizations are required to treat TPN-related complications

B. The development of progressive but reversible liver failure

C. Inability to maintain venous access

III. Living Donor

A. A small bowel transplant using a living donor may be considered **medically necessary** only when a cadaveric intestine is not available for transplantation in a patient who meets the criteria noted above for a cadaveric transplant (I-II).

B. A small bowel transplant using living donors is considered **not medically necessary** in all other situations.

IV. A small bowel retransplant is considered **medically necessary** after a failed small bowel transplant.

V. A small bowel transplant is considered **not medically necessary** for patients with intestinal failure who are able to tolerate TPN.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

CROSS REFERENCES

1. Small Bowel/Liver and Multivisceral Transplant, Transplant, Policy No. 18

BACKGROUND

Intestinal failure is a serious medical condition which results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance.[1] Short bowel syndrome, one type of intestinal failure, is a condition in which the absorbing surface of the small intestine is inadequate due to extensive disease or surgical removal of a large portion of small intestine. Etiologies of short bowel syndrome include: volvulus, atresias, necrotizing enterocolitis, gastroschisis, desmoid tumors, and trauma. Patients with short bowel syndrome are unable to obtain adequate nutrition from enteral feeding and become dependent upon total parenteral nutrition (TPN). Patients with complications from TPN, such as catheter-related mechanical problems, infections, hepatobiliary disease, and metabolic bone disease, may be considered candidates for small bowel transplant.

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Intestinal transplants, including multivisceral and bowel/liver, represent a small minority of all solid organ transplants. In 2015 and 2016, 141 and 147 intestinal transplants, respectively, were performed in the United States, of which all but two were from deceased donors.[2] While cadaveric intestinal transplant is the most commonly performed transplant, there has been more recent interest in using living related donors. Potential advantages of a living donor include the ability to plan the transplant electively and better antigen matching, leading to improved management of rejection.

EVIDENCE SUMMARY

Ideally, for intestinal transplant to be considered as a replacement for total parenteral nutrition (TPN), head-to-head comparisons of transplantation versus TPN are needed, preferably in well-designed randomized controlled trials (RCTs). Further, for chronic conditions such as intestinal failure, comparative trials with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects, and to establish guidelines regarding the timing of intestinal transplant. In order to establish the net benefit of using living donors versus cadaveric intestinal transplant for treatment of intestinal failure, clinical trials that compare these therapies are needed, and the impacts on health outcomes for both the donors and recipients must be considered.

The current literature on small bowel transplantation included the following general observations:

- The importance of timely referral for intestinal transplantation was emphasized to avoid the necessity of combined liver and intestine transplantation.
- While outcomes continue to improve, obstacles to long-term survival remain. Recurrent and chronic rejections and complications of immunosuppression are significant issues in bowel transplantation.
- It has been suggested that improvements in survival over the last 10–15 years may justify removing the restriction of intestinal transplantation to patients who have severe complications of TPN.[3] However, as noted by Vianna in their report on the status of intestinal transplantation, no randomized trials compare intestinal transplantation to long-term parenteral nutrition, and optimal timing for earlier transplantation has not been established.[4]

SYSTEMATIC REVIEWS

This policy was initially based on 1995 and 1999 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessments.[5,6] The 1995 assessment concluded that in children, small bowel transplant was associated with improved survival compared to TPN. This assessment also concluded that in adults, the outcomes for small bowel transplant were worse than those associated with TPN.

The 1999 TEC assessment reevaluated the data on adults, specifically focusing on the probability of adult patient and graft survival with small bowel transplant compared to TPN, and whether successful outcome of small bowel transplant improves health outcomes or reduces adverse outcomes.[6] The assessment reported that bowel transplants in adults produce patient survival rates from 27%-58% at 4 or 5 years. Graft survival rates (and presumably independence from TPN) range from 13%-30%. It is unknown whether this represents a net benefit to these patients, since some patients may survive for long periods of time on TPN. The TEC assessment also indicated that some patients with increasingly severe TPN-

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associated complications may face a high probability of impending mortality such that the risk of continued medical management is higher than the risk of transplantation. However, at this point in time, it is not possible to predict which patients will survive longer on TPN versus small bowel transplant.

In 2010, Sudan published a systematic review of current literature on long-term outcomes after intestinal transplantation.[7] The author noted that intestinal transplantation has become standard therapy for patients with life-threatening complications from parenteral nutrition therapy. Data from current single-center series indicate a 1-year patient survival rate of 78-85% and a 5+ year survival rate of 56-61%. With respect to pediatric intestinal transplant patients, the majority achieve normal growth velocity at two years post-transplant. However, oral aversion is a common problem; tube feedings are necessary in 45% of children. Sudan also noted that parental surveys of quality of life in pediatric transplant patients have shown that intestinal transplant patients appear to have modestly improved quality of life compared to patients remaining on TPN and slightly worse than matched school-age controls without intestinal disease.

RANDOMIZED CONTROLLED TRIALS

No RCTs were identified that compared intestinal transplantation with ongoing parenteral nutrition with or without subsequent small bowel/liver or multivisceral transplantation.

NONRANDOMIZED STUDIES

Despite the lack of RCTs, isolated small bowel transplantation has become an accepted alternative to continued total parenteral nutrition (TPN) to avoid the need for multivisceral transplantation in carefully selected patients with intestinal failure who are developing severe complications related to total parenteral nutrition (TPN).

The following is a summary of non-randomized trials that are representative of the available data on small bowel transplantation from living donors and post-transplantation complications.

Living Donor

The literature related to living-related intestinal transplant consists of small case reports of 1 to 11 patients in which different lengths of the ileum or jejunum were used.[8-15] While there appeared to be minimal complications to the donors, of the cases reported a significant number of recipients remained on TPN for at least part of their nutrition while others remain healthy and off TPN.

Ueno reported on 21 intestinal transplant patients that underwent transplantation between 1996 and 2012 at one of five institutions.[16] Twelve transplants came from living donors. All but one patient received an isolated small bowel transplant for intestinal failure. The overall 1- and 5- year survival rates were 86% and 68%, respectively. In the 15 patients who underwent transplantation after 2006, 1-year survival was 92% and 5-year survival was 83%.

Gangemi and Benedetti published a literature review of living donor small bowel transplantation reports from 2003 to 2006; all of the reports listed Benedetti as author.[17] The authors commented that, “Due to the excellent result in modern series of deceased donor bowel transplantation, widespread use of the procedure [living donor] should not be recommended, in consideration of the potential risks to donor. Furthermore, few centers have acquired the necessary experience with the procedure.” Benedetti also reported outcomes

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from 4 children and 7 adults who underwent 12 living-related small bowel transplantations between 1998 and 2004.[18] All donors were reported to have had uneventful recovery following removal of up to 40% of the small intestine. The 3-year patient survival was 82%, with graft survival of 75%. Longer follow-up from the earlier cases was not reported.

Complications

In 2016, Limketkai published a retrospective study on mortality and graft rejection rates in 1115 cases of intestinal transplants performed from May 1990 through June 2014.[19] Of these, 142 transplants were done for Crohn's disease (CD). Transplants were rejected in 33.3% of patients without CD and 36.9% of patients with CD. The actuarial risk of death for patients with CD at one, five, and ten years post-transplant 22.5%, 50.3%, and 59.7%, respectively. Patients without CD had similar mortality risks.

In 2014, Calvo Pulido reported on 21 adults who underwent intestinal transplantation; 17 were isolated small bowel transplants.[20] Thirteen patients (62%) experienced renal failure; the etiology included high ileostomy output, immunosuppression and medical treatment.

In 2013, Boyer reported that 7 of 12 children who had an isolated small bowel transplant had renal function complications at some point after surgery.[21] Prior to treatment, all of the patients had normal renal functioning.

Florescu have published several articles retrospectively reviewing complications in a cohort of 98 pediatric patients. Twenty-one of these children (21.4%) had an isolated small bowel transplant; the remainder had combined transplants. These articles include a 2012 study that reported that 68 of the 98 patients (69%) developed at least one episode of bloodstream infection.[22] Among the patients with an isolated small bowel transplant, the median time to infection for those who became infected was 4.5 months (95% confidence interval [CI]: 2.4 to 6.7 months). Also in 2012, the researchers reported that 7 of 98 patients (7%) developed cytomegalovirus (CMV) disease; only one of these had an isolated small bowel transplant.[23] A 2010 study by this group retrospectively reported on the incidence of fungal infection after pediatric small bowel transplantation among patients treated between 2003 and 2007 at a single center.[24] The average length of follow-up was not reported. A total of 25 of 98 cases reviewed (26%) developed at least one episode of fungal infection; Candida infection was most common. During the study period, the mortality rate did not differ significantly between patients who did and did not develop a fungal infection (32.3% vs. 29.8%, respectively), but the authors stressed the importance of better screening tools to identify and prevent fungal infections.

As noted previously, Sudan reported oral aversion to be a common problem in pediatric patients with tube feedings necessary in 45% of children following small bowel transplantation.[7]

Retransplantation

Desai have published the most comprehensive reporting of outcomes after repeat small bowel transplant in the United States. A 2012 publication evaluated data in the UNOS database on patients who underwent small bowel transplants in the U.S between October 1987 and August 2009.[25] The investigators identified 41 repeat isolated small bowel transplants in adults and 28 in children. Thirty-nine of the adults (95%) and 27 (96%) of the children had a previous isolated small bowel transplant; the remaining patients had an initial combined small bowel and liver transplant.

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Among adults, survival rates after retransplant were 80% after 1 year, 47% after 3 years and 29% after 5 years. Comparable survival rates for primary isolated small bowel transplant were 84% after 1 year, 67% after 3 years and 54% after 5 years. Survival was significantly lower after repeat isolated small bowel transplant compared to primary isolated small bowel transplant, p=0.005.

Among children, patient survival was 81% after 1 year, 74% after 3 years and 58% after 5 years. These rates did not differ significantly from rates after primary isolated small bowel transplant (85% after 1 year, 71% after 3 years and 64% after 5 years, respectively).

HIV POSITIVE TRANSPLANT RECIPIENTS

This subgroup of recipients has long been controversial due to the long term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. Although HIV positive transplant recipients may be a research interest of some transplant centers, the minimal data regarding long term outcomes in these patients consist primarily of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons would argue that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease.

The Organ Procurement and Transplantation Network (OPTN) considers HIV+ organ candidates to be acceptable recipients "if permitted by the transplant hospital. Care of HIV test positive organ candidate and recipients should not deviate from general medical practice."[26]

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)

The AGA issued a medical position statement on short bowel syndrome and intestinal transplantation citing that intestinal transplants have only been performed in patients with life-threatening complications attributable to their intestinal failure and long-term TPN therapy and that standards of care for this type of transplantation are still evolving.[27]

SUMMARY

There is enough research to show that small bowel transplants can improve health outcomes in certain patients with intestinal failure with serious complications from total parenteral nutrition (TPN). Therefore, isolated small bowel transplant may be considered medically necessary in patients that meet the policy criteria.

There is enough research to show that small bowel transplant does not improve health outcomes in patients with intestinal failure who are able to tolerate TPN. Therefore, small bowel transplant may be considered not medically necessary for these patients.

There is enough research to show that small bowel retransplant improves health outcomes in patients that have had a failed small bowel transplant. Therefore, for patients with failed small bowel transplant, retransplant may be considered medically necessary.

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CODES

Codes	Number	Description
CPT	44132	Donor enterectomy (including cold preservation), open; from cadaver donor
	44133	Donor enterectomy (including cold preservation), open partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
HCPCS	None	

Date of Origin: *January 1996*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 13

Islet Transplantation

Effective: June 1, 2020

Next Review: March 2021
Last Review: April 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Islet cells are responsible for producing insulin, which is necessary for the regulation of blood glucose levels. Following islet transplantation, it is proposed that the beta cells in the transplanted islets will begin to make and release insulin.

MEDICAL POLICY CRITERIA

I. Autologous pancreas islet cell transplantation may be considered **medically necessary** as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

II. Autologous pancreas islet cell transplantation for all other indications is considered **investigational**.

III. Allogeneic and xeno islet cell transplantation for any diagnosis are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

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It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Pancreas Transplant, Transplant, Policy No. 6

BACKGROUND

CHRONIC PANCREATITIS

Although the incidence of chronic pancreatitis is rising, it is still a relatively rare condition, affecting an estimated seven to eight new people out of every 100,000 people each year.[1] Some patients with chronic pancreatitis may experience intractable pain that can only be relieved with a total or near-total pancreatectomy. However, the pain relief must be balanced against the certainty that the patient will be rendered an insulin-dependent diabetic. Autologous islet cell transplantation, also called islet autotransplantation (IAT), has been investigated as a technique to prevent this serious morbidity.

TYPE 1 DIABETES

Glucose control is a challenge for individuals with type 1 diabetes. Failure to prevent disease progression can lead to long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease.

ISLET TRANSPLANTATION

In autologous islet transplantation during the pancreatectomy procedure, islet cells are isolated from the resected pancreas using enzymes, and a suspension of the cells is injected into the portal vein of the patient's liver. Once implanted, the beta cells in these islets begin to make and release insulin.

Allogeneic islet cell transplantation is normally conducted as a stand-alone procedure among patients with type 1 diabetes. Islet cells, harvested from a deceased donor's pancreas, are processed and injected into the recipient's portal vein.

Allogeneic islet cell transplantation potentially offers an alternative to whole-organ pancreas transplantation to treat type 1 diabetes, restore normoglycemia and ultimately reduce or eliminate the long-term complications of diabetes, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. However, a limitation of islet cell transplantation is that two or more donor organs are usually required for successful transplantation, and only pancreases rejected for whole-organ transplant are typically used for islet transplantation. Due to limited islet cell supply, allogeneic islet cell transplantation is recommended only for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management. In 2000, a modified immunosuppression regimen increased the success of allogeneic islet transplantation. This regimen was developed in Edmonton, Canada and is known as the "Edmonton protocol."

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While most of the published research to date involves the transplantation of allogeneic human islet cells, there is also interest in xenotransplantation, using porcine islet cells.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Allogeneic islet cells are included in these regulations.

EVIDENCE SUMMARY

AUTOLOGOUS ISLET CELL TRANSPLANT AS AN ADJUNCT TO PANCREATECTOMY

Autologous islet cell transplantation as an adjunct to pancreatectomy or near total pancreatectomy among patients with chronic pancreatitis has been investigated since 1977. Since then, the experience has grown slowly with incremental improvements in the islet cell isolation process. The focus of this section is on systematic reviews.

Systematic Reviews

In 2015, Wu published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis.[3] Studies could use any type of design but needed to include at least five patients or have a median follow-up of at least six months. Twelve studies with a total of 677 patients met the review's inclusion criteria. The mean age of the patients was 38 years and mean duration of pancreatitis was 6.6 years. A meta-analysis of the insulin independence rate at one year (five studies, 362 patients) was 28.4% (95% confidence interval [CI], 15.7% to 46.0%). At two years, the pooled insulin independence rate (three studies, 297 patients) was 19.7% (95% CI, 5.1% to 52.6%). The pooled 30-day mortality rate (11 studies) was 2.1% (95% CI, 1.2% to 3.8%). Long-term mortality data were not pooled.

In 2012, Bramis searched for studies reporting on patients who had been treated with total, subtotal or completion pancreatectomy followed by islet autotransplantation.[4] Case series were included if they included more than five individuals and reported outcomes for consecutive patients. A total of 72 full-text articles were reviewed, and five studies were found to meet inclusion criteria. The postoperative insulin independence rate in the five studies ranged from 10% (mean follow-up of eight years) to 46% (mean follow-up of five years). In the study with the longest follow-up, the insulin independence rate was 28% at ten years. Two studies reported postoperative morphine use with a decrease in morphine use of 116 mg and 55 mg, respectively.

A 2011 systematic review by Dong included studies regardless of design or sample size.[5] After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11 studies of total pancreatectomy, two studies of partial pancreatectomy, and two studies that included both types of surgery. Sample sizes in individual studies ranged from three to 173 patients. Thirteen studies included patients with chronic pancreatitis, and two included patients with benign pancreatic tumors. The pooled 30-day mortality was 5% (95% confidence interval [CI]: 2 to 10%), and the cumulative mortality at one year (reported by ten studies) was 4.9% (95% CI: 2.6 to 7.3%) In a pooled analysis of data from 14 studies, the rate of insulin dependence at last follow-up was 4.6 per 100-person years (95% CI: 1.53 to 7.62). The pooled rate of insulin independence at one year (five studies) was 27% (95% CI: 21-33%)

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and at two years (three studies) was 21% (95% CI: 16-27%).

ALLOGENEIC ISLET CELL TRANSPLANT FOR TYPE 1 DIABETES

Islet cell transplantation has also been investigated as a treatment for type 1 diabetes, particularly in patients with poor glucose control despite insulin therapy.

The principal outcomes associated with treatment of type 1 diabetes are improvement in overall mortality rate, and reductions in rates of diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease normally associated with type 1 diabetes. In order to understand the impact of islet cell transplantation for treatment of type 1 diabetes on these outcomes, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as insulin treatment, are needed. Further, an understanding of any adverse treatment effects, particularly those associated with life-long immunosuppressant therapy, must be carefully weighed against any benefits associated with islet transplantation to understand the net treatment effect of this therapy.

Systematic Reviews

In 2015 Health Quality Ontario published a systematic review on islet transplantation for type 1 diabetes, and included one health technology assessment, 11 observational, nonrandomized clinical studies, one registry report, and four guidelines.[6] There was a large degree of heterogeneity in patient populations, study design, and outcome measurement in the included studies. The reviewers reported that islet transplantation can improve blood sugar control and quality of life, and may reduce diabetic complications; however, the results were inconsistent between studies. Compared with insulin therapy, there were more adverse events with islet transplantation. The studies that were included that assessed health-related quality of life, secondary complications of diabetes, glycemic control, and adverse events were all ranked as low to very low quality, with two studies having high risk of bias. Therefore, uncertainty of the effectiveness of islet transplantation in type 1 diabetics still remains.

Randomized Controlled Trials

An open-label randomized controlled trial (RCT) was published by Lablanche in 2018 evaluating patients who had type 1 diabetes with severe hypoglycemia or in kidney transplant patients following transplantation.[7] A total of 50 patients with severe hypoglycemia, hypoglycemia unawareness, or kidney grafts with poor glycemic control received immediate islet transplantation (n=25) or intensive insulin therapy followed by delayed islet transplantation (n=22). Median follow-up was six months for both groups. The primary end point was a composite score (β score) which has not been validated and which reflected fasting glucose, HbA1c level, C-peptide, and insulin independence. The proportion of patients with a modified β-score of 6 or higher at six months was 64% of patients in the immediate transplantation group and 0% in the control group ($p<0.001$). Of note, few patients in the insulin group used continuous glucose monitoring or other technologies to monitor for hypoglycemia. At six months, insulin independence was achieved in 44% of patients in the immediate transplantation group ($N = 25$; $p = 0.0004$). After the entire cohort received islet transplantation, the one-year insulin independence rate was 59% ($N = 46$; $p < 0.0001$). Negative effects reported at 12 months included bleeding complications in 7% of patients and a decrease in median glomerular filtration rate from 90.5 mL/min to 71.8 mL/min in islet transplant patients who had not previously received a kidney graft and from 63.0 mL/min to 57.0 mL/min in islet transplant patients who had previously received a kidney graft. Trial

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limitations included possible bias from open-label design as well as an inadequate follow-up period to demonstrate transplant durability.

Froud randomized 16 type 1 diabetes mellitus patients to evaluate cultured islet transplantation with or without tumor necrosis factor (TNF-alpha) blockade using Infliximab just prior to islet infusion.[8] Insulin independence was achieved in 14 patients after one to two infusions, and was maintained in 11 patients after one year, and in six patients at 33 +/- 6-months without additional infusions. The authors reported no identifiable clinical benefit with the use of Infliximab, but concluded cultured human islet allografts produced results comparable to freshly transplanted islets including normalization of HBA1c. Further research in larger studies is needed to explore different immunosuppressive regimens.

Nonrandomized Studies

Holmes-Walker (2017) performed a within-subject paired comparison to examine the efficacy of insulin injections and islet transplantation to reduce hypoglycemia and glycemic variability in type 1 diabetes patients with severe hypoglycemia.[9] Ten patients with type 1 diabetes were initially treated with insulin injections delivered as multiple daily injections (MDI). Patients then switched to continuous subcutaneous insulin infusion (CSII) and remained on CSII until islet transplantation. The authors completed a within-subject, paired comparison of MDI and CSII and CSII and 12 months post-islet transplantation. Following the switch from MDI to CSII, the average Edmonton Hypoglycemia Score (HYPOscore) reduced significantly, from 2028 to 1085 ($p<0.05$), hypoglycemia events reduced significantly from 24 to 8 per patient-year ($p<0.05$), the standard deviation of glucose and continuous overlapping net glycemic action using a four-hour interval (CONGA4) reduced significantly ($p<0.05$), and HbA1c, mean glucose and median percent time hypoglycemic were unchanged. Twelve months post-islet transplantation, compared to CSII, there were significant reductions in HbA1c, median HYPO score, mean glucose, standard deviation of glucose, and CONGA4.

In 2015 Caiazzo assessed procedure-related complications on long-term outcome of islet transplantation in 26 patients with type 1 diabetes.[10] Each patient had two to three intraportal islet infusions, performed surgically or under ultrasound guidance, within a three-month time frame. Complications included: bowel obstruction, biliary peritonitis and a major hepatic hematoma. The investigators reported no deaths or patient dropouts. Early complications occurred in nine of 68 procedures. Procedure-related complications negatively impacted graft function ($p = 0.009$) and was an independent negative predictor of long-term graft survival ($p = 0.033$) in multivariate analysis. The investigators concluded that even nonsevere complications occurring during islet transplantation, despite islet preparation method or transplantation method, significantly impair primary graft function and graft survival.

Moassesfar (2016) compared safety and efficacy of islet cell transplantation to pancreas transplantation at a center in the U.S.[11] Sequential patients with type 1 diabetes had either an islet cell transplant ($n = 10$) or a pancreas transplant ($n = 15$). After one year, 90% of patients in the islet group and 93% of patients in the pancreas group were insulin independent. At three years, the proportion with insulin independence dropped to 70 % and 64%, respectively. The authors concluded that islet cell transplantation can produce similar outcome to pancreatic transplantation.

In 2013, Rickels reported on 12 patients with type 1 diabetes and severe hypoglycemia who had islet transplantation.[12] Mean glycosylated hemoglobin decreased from 7.0%±0.3% before the procedure to 5.6%±0.1% after six to seven months ($p<0.01$). All of the insulin sensitivity

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measures were significantly less than normal before islet transplantation and not significantly different from normal after transplantation. Adverse events were not discussed.

In 2013, O'Connell reported on 17 patients who underwent islet transplantation for type 1 diabetes and severe hypoglycemia.[13] The primary end point was the proportion of patients who had had an HbA1c less than 7% and no severe hypoglycemic events two months after the initial transplant. (Patients could have one or two infusions.) Fourteen of the 17 (82%) patients achieved the primary end point. Nine (53%) patients attained insulin independence for a median of 26 months. At the time of data analysis for this publication, six patients remained insulin independent. Most adverse events were related to immunosuppression. Seven of the 17 (41%) patients developed mild lymphopenia and one developed Clostridium difficile colitis; these all responded to treatment. Eight patients developed anemia shortly after transplant and one required a blood transfusion. Procedure-related complications included one partial portal vein thrombosis and three postoperative bleeds; two of the bleeds required transfusion. Patients were followed for different amounts of time; long-term follow-up data were not available for a consistent length of time.

In 2012, Vantyghem reported on 23 patients with type 1 diabetes who underwent islet transplantation; 14 had islet-only transplants and nine had islet after kidney transplants.[14] Median HbA1c was 8.3% at baseline and 6.7% at three years. Ten of the 23 patients (43%) were insulin independent three years after islet transplantation. Findings were not reported separately for the islet-only transplant recipients.

In 2011 Thompson reported on a prospective cross-over study of intensive medical therapy (pre-transplant) versus islet cell transplantation among 32 patients with type 1 diabetes.[15] Following enrollment in the study, median follow-up was 47 months pre-transplant and 66 months post-transplant. Although improvements in HbA1c, retinopathy progression, and renal function were seen in the transplant group, small sample size and lack of treatment randomization limit interpretation of these findings. The authors also noted that their finding of reduced microvascular complications after islet transplantation may be due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil (MMF).

In 2006, Shapiro reported on 36 patients with type 1 diabetes mellitus that had undergone islet transplantation.[16] While short-term results were promising, insulin independence was generally not sustainable; only five patients were insulin-independent at two years. In a landmark study known as the Edmonton Protocol, seven consecutive patients achieved insulin independence following islet cell transplants from two to four donors on a glucocorticoid-free immunosuppressive regimen.[17] However, 5-year outcomes from the first patients transplanted under the Edmonton protocol reported less than a 10% rate of insulin independence at five years, despite persistent graft survival as measured by C-peptide positivity (~80%).[18] The authors noted that problems with glycemic lability and hypoglycemia, the primary indications for transplant, were corrected; however, no clear advantages for chronic complications of diabetes (e.g., peripheral neuropathy) were evident. Chronic complications related to standard immunosuppressive therapy led to the need to alter the protocol in 23% of patients, thus leading the authors to conclude that "safer immunosuppression associated with fewer side effects is needed." Complications and side effects related to both immunosuppression and the procedure itself are also reported to be more common than originally thought.[19] The experience of the transplant center itself has a demonstrated effect on patient outcomes, with the more experienced centers reporting higher success rates.

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Long-term results from the Edmonton Protocol were published by Brennan (2016), who reported that all seven of the original subjects continued to have some islet function more than ten years after the transplantation.[20] One of the patients achieved insulin independence for eight years, but had graft failure 10.9 years after the first transplant. Of the other six subjects, three received an additional islet transplant, five were receiving insulin, and two were insulin-independent (with one taking liraglutide). None of the subjects had lymphoma, severe hypoglycemia, or opportunistic infections during follow-up.

Several other small case series have focused on identifying alternatives to current transplant techniques, studying encapsulated islet transplantation without immunosuppression,[21] optimizing single versus multiple-donor transplantations,[22] and comparing whole pancreas transplant to islet cell transplantation.[23,24] Recent research also addresses islet-after-kidney transplantation.[25] However, results from these studies should be interpreted with caution as the small sample sizes (n≤ 66), lack of randomized treatment allocation and/or appropriate comparison groups do not allow for ruling out chance as an explanation of findings.

Current non-randomized studies of allogeneic islet cell transplantation appear to suggest an initial benefit (such as a decline in HbA1c levels, for example) associated with the transplant. However, as a 2010 review of this therapy notes:[26]

> "[O]ne cannot be certain of the claim that partially failed islet transplantation leads to the use of less insulin and less hypoglycemia on a cause-effect basis. It could just as easily be that patients who enter transplant programs come under close clinical scrutiny by interested diabetologists who begin managing them more skillfully."

Additional randomized controlled trials are needed to determine the strength and magnitude of potential benefits associated with this therapy and to isolate such the impact of such benefits from standard medical care.

REGISTRY DATA

Bretzel reported in 2007 data collected from the International Islet Transplant Registry from 1999-2004.[27] Data were available for 458 human islet cell transplantations. At 1-year post transplant, patient survival was 97%, islet grafts were functioning in 82% of the cases, and insulin independence was achieved in 43% of the cases.

Founded in 2001 by the National Institute of Diabetes, Digestive and Kidney Diseases, the Collaborative Islet Transplant Registry (CITR) has been collecting information on allogeneic islet transplantation in North America, Europe, and Australia. The most recent peer-reviewed publication of CITR data was published in 2012.[28] The update focused on changes in outcomes over time in 677 patients, all of whom received a transplant as of December 31, 2010 (n=575 islet-only; n=102 kidney+islet). Unfortunately, outcomes presented in this report were limited by considerable levels of missing data which increased with longer follow-up. The missing data were reported to be a mixture of unavailable medical records and data still pending entry into the registry.

The authors reported improved insulin independence at three years post-transplant, from 27% in the early era (1999–2002, n = 214) to 37% in the mid era (2003–2006, n = 255) and 44% in the most recent era (2007–2010, n = 208; P = 0.006 for years-by-era; P = 0.01 for era alone). However, not all recipients in the latter era had reached the three-year milestone at the time of this updated report. The need for islet reinfusion for loss of function of first graft by one-year

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decreased significantly from 60-65% in 1999-2006 to 48% in 2007-2010 ($p<0.01$). There was also a modest decrease in clinically reportable adverse events in the 2007-2010 era, from 50-53% in 1999-2006 to 38% in 2007-2010. The rates of peritoneal hemorrhage or gallbladder infusion were 5.4% in 1999-2003 and 3.1% in 2007-2010. The authors did not report findings separately from the subset of patients who underwent islet-only transplants.

The Institute for Clinical and Experimental Medicine (IKEM), based in the Czech Republic, published results from a retrospective analysis of a registry of all patients receiving one or more allogeneic or autologous islet transplants from 2005 to 2010 (n=15 and n=5, respectively).[29] Although islet function was documented in 11 of 15 and three of five patients, respectively, after 12 months (as indicated by C-peptide levels), only one patient receiving an allogeneic transplant was able to achieve independence from insulin beyond 12 months. The authors conclude that islet transplant may be best suited for high-risk recipients, as “routine clinical application is still hampered by the limited availability of usable organ transplants and viability of transplanted islets.”

Results from the above registry reports should be interpreted with caution as these registries are not reflective of the complete North American experience with islet transplants; not all transplant centers participated in each regional endeavor, nor is data complete for all those who do participate. Therefore, there may be inherent bias in the data. The focus on intermediate outcomes instead of long-term health outcomes, also limits interpretation of these findings.

XENOTRANSPLANTATION

Although there is research interest in porcine islets as an alternative and potentially unlimited source of islet cells, current data from human clinical trials is limited to three case series.

Matsumoto (2016) transplanted two doses of encapsulated neonatal porcine islets (approximately 5000IEQ/kg and 10,000IEQ/kg) twice in two groups of four patients each with type 1 diabetes.[30] The two transplants were performed three months apart. One patient had a serious adverse event potentially related to the treatment, paralytic ileus, which was resolved with medication. While both groups had decreases in HbA1c, for the high dose group this difference remained significant at 600 days after the first transplant.

In 2011, Wang published results from a small clinical trial on the safety and feasibility of neonatal porcine islets (NPIs) in 22 patients in China.[31] However, only six of the 22 patients were subsequently followed for more than two months, limiting conclusions about the long-term use of NPIs.

Also in 2011, Esquivel-Pérez published a report on 23 patients not on immunosuppression, transplanted with a porcine cell-filled device.[32] Following an average of 5.7 years post-transplantation, the researchers reported that the patients with the lowest levels of antibodies were significantly more likely to report higher insulin dose reductions. However, not all patients were able to attain low levels of antibodies, for reasons not clearly known. Therefore, this report provides evidence for transplantation protocols but does not address the clinical utility of xenotransplantation.

Current literature has not directly addressed problems related to xenograft rejection and xeno-zoonosis (transmission of animal disease to humans).

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PRACTICE GUIDELINE SUMMARY

In 2019, the American Diabetes Association (ADA) updated their position statement on comprehensive care for patients with type 1 diabetes.[33,34] The statement includes a recommendation with a C rating stating that "Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes." In addition, it states:

> "Pancreas and islet cell transplantation have been shown to normalize glucose levels but require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal ztransplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite aggressive glycemic management."

SUMMARY

There is enough research to show that autologous islet cell transplantation is relatively safe and can reduce the chance of developing diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. Therefore, autologous islet cell transplantation may be considered medically necessary as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

There is not enough research to show that autologous islet cell transplantation can improve health outcomes for people with any other conditions. Therefore, autologous pancreatic islet cell transplantation for all other indications is considered investigational.

Although there is research interest in porcine islets (xeno islet cells) as a source of islet cells and allogeneic transplantation, there is not enough research to show that xenotransplantation or allogeneic transplantation is safe and effective, and there are no clinical guidelines based on research that recommend xenotransplantation or allogeneic transplantation. Therefore, xeno islet cell transplantation and allogeneic islet transplantation for any diagnosis are considered investigational.

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CODES

Codes	Number	Description
CPT	0584T	Percutaneous islet cell transplant, includes portal vein catheterization and Infusion
	0585T	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
	0586T	Laparoscopy for islet cell transplant, open approach
	48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islets
	48999	Unlisted procedure, pancreas
HCPCS	G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
	G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
	G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion
	S2102	Islet cell tissue transplant from pancreas; allogeneic

Date of Origin: *January 1996*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 18

Small Bowel/Liver and Multivisceral Transplant

Effective: June 1, 2020

Next Review: March 2021
Last Review: May 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Small bowel/liver transplantation is performed in patients that have both intestinal and liver failure and may be combined with the transplantation of other portions of the digestive tract and accessory organs.

MEDICAL POLICY CRITERIA

I. A small bowel/liver transplant or multivisceral transplant may be considered **medically necessary** for pediatric and adult patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance), who have been managed with long-term total parenteral nutrition and who have developed evidence of impending end-stage liver failure, when transplant candidates meet both of the following criteria:
   A. Adequate cardiopulmonary status; and
   B. Documentation of patient compliance with medical management.

II. A small bowel/liver transplant or multivisceral transplant may be considered **not medically necessary** when Criterion I. is not met.

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III. A small bowel/liver retransplant or multivisceral retransplant may be considered **medically necessary** after a failed primary small bowel/liver transplant or multivisceral transplant.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Liver Transplant, Transplant, Policy No. 5
2. Isolated Small Bowel Transplant, Transplant, Policy No. 9

BACKGROUND

Small bowel/liver transplantation is transplantation of an intestinal allograft in combination with a liver allograft, either alone or in combination with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, or colon. Small bowel transplants are typically performed in patients with intestinal failure due to functional disorders (e.g., impaired motility) or short bowel syndrome, defined as an inadequate absorbing surface of the small intestine due to extensive disease or surgical removal of a large portion of small intestine.

In some instances, short bowel syndrome is associated with liver failure, often due to the long-term complications of total parenteral nutrition (TPN). These patients may be candidates for a small bowel/liver transplant or a multivisceral transplant, which includes the small bowel and liver with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, and/or colon. A multivisceral transplant is indicated when anatomic or other medical problems preclude a small bowel/liver transplant, and the patient requires removal of all of the native gastrointestinal tract and replacement with a multivisceral graft.

Note: Isolated small bowel transplants and isolated liver transplants are considered in separate medical policies (see Cross References section above).

EVIDENCE SUMMARY

Much of the published literature consists of case series reported by single centers. Authors of these reports as well as narrative reviews observed that while outcomes continue to improve, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long term survival.

REGISTRY DATA

The most recent published report from the international Intestinal Transplant Registry (ITR) reported on 2,887 transplants in 2,699 patients from 82 transplant programs worldwide.[1]

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Participation in this registry was considered to be nearly 100% of all intestinal transplants performed in the world since April 1985. The following results were reported:

- Regional practices and outcomes are now similar worldwide.
- Current actuarial patient survival rates at one-, five-, and 10-years post-transplant are 76%, 56%, and 43%, respectively.
- Outcomes of intestinal transplantation improved modestly over the past decade, but rates of graft loss beyond one year have not improved.
- The reasons for late graft loss have been difficult to identify due to the low case volumes at most centers.
- Better function was found in intestinal grafts that included a colon segment and/or a liver component.

Better graft survival was also seen in patients who waited at home for intestinal transplant, used induction immune-suppression therapy, and had rapamycin maintenance therapy.

NON-RANDOMIZED TRIALS

Survival Outcomes

The published literature consists of case series, mainly reported by single centers in the United States and Europe. Tables 1 and 2 summarize the characteristics and results of the case series, respectively. Many case series have included isolated small bowel transplantations.

Reasons for transplantations were mainly short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off total parenteral nutrition (TPN). Several studies have presented survival rates by type of transplantation, while others have combined all types of transplants when reporting survival rates. When rates were reported by type of transplant, isolated transplantations had higher survival rates than multivisceral transplants (see Table 2).

Several investigators have reported higher survival rates in transplants conducted more recently than those conducted earlier.[2-4] Reasons for improved survival rates in more recent years have been attributed to the development of more effective immunosuppressive drugs and the learning curve for the complex procedure.

Authors of these series, as well as related reviews, have observed that while outcomes have improved over time, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long-term survival. A separate discussion of complications follows the evidence tables.

Table 1. Summary of Key Case Series Characteristics for Transplantations[5]

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range)
				Treatment	n	
Elsabbagh (2019)[6]	United States	174		• Isolated IT • Combined liver IT • Multivisceral graft • Modified multivisceral	98 44 28 4	>3 y

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Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range)
				Treatment	n	
Lacaille (2017)[7]	France	110	5.3 (0.4-19)	• Isolated IT • Combined liver IT • Multivisceral graft	45 60 5	Of 55 alive: • 17 at <5 y • 17 at 5-10 y • 21 at ≥10 y
Garcia Aroz (2017)[8]	United States	10	1.5 (0.7-13)	• Isolated IT • Combined liver IT	7 3	6/7 alive at follow-up ≥10 y
Dore (2016)[9]	United States	30	0.2 (0.1-18)	• Isolated IT • Combined liver IT • Multivisceral graft	6 6 18	28 (4-175) mo
Rutter (2016)[10]	United Kingdom	60	1.8 (0-8)	• Isolated IT • Multivisceral graft • Modified multivisceral	16 35 9	21.3 (0-95) mo
Lauro (2014)[11]	Italy	46	34 (NR)	• Isolated IT • Combined liver IT • Multivisceral graft	34 6 6	51.3 mo
Varkey (2013)[12]	Sweden	20	Adults: • 44 (20-67) Children: • 6 (0.5-13)	• Isolated IT • Combined liver IT • Multivisceral graft	4 1 15	NR
Mangus (2013)[2]	United States	100	Adults: • 48 (NR to 66) Children: • 1 (0.6 to NR)	• Multivisceral graft • Modified multivisceral	84 16	25 mo

IT: intestinal transplantation; NR: not reported.
[a] Living donors.

Table 2. Summary of Key Case Series Results for Transplantations[5]

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Elsabbagh (2019)[6]	• Isolated IT • Combined liver IT • Multivisceral graft • Modified multivisceral	98 44 28 4	All transplantations combined: • 69.5% at 3 y • 66% at 5 y • 63% at 10 y	NR
Lacaille (2017)[7]	• Isolated IT • Combined liver IT • Multivisceral graft	60 45 5	• 59% at 10 y; 54% at 18 y • 48% at 10 y • NR	All treatments combined: • 73% at last follow-up
Garcia Aroz (2017)[8][a]	• Isolated IT • Combined liver IT	7 3	All transplantations combined: • 70%	All treatments combined: • 100% at last follow-up
Dore (2016)[9]	• Isolated IT • Combined liver IT • Multivisceral graft	6 6 18	• 83% at 9 y • 33% at 10 y • 67% at 2.5 y	All treatments combined: • 71% in 31 d • 62% at last follow-up
Rutter (2016)[10]	• Isolated IT • Multivisceral graft	16 35 9	• 92% at 1 y; 37% at 5 y • 71% at 1 y; 33% at 5 y • 85% at 1 y; 65% at 5 y	NR

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Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
	• Modified multivisceral			
Lauro (2014)[11]	• Isolated IT • Combined liver IT • Multivisceral graft	34 6 6	All transplantations combined: • 77% at 1 y • 58% at 3 y • 53% at 5 y • 37% at 10 y	NR
Varkey (2013)[12]	• Isolated IT • Combined liver IT • Multivisceral graft	4 1 15	All transplantations combined: • 78% at 1 y • 50% at 5 y	NR
Mangus (2013)[2]	• Multivisceral graft • Modified multivisceral	84 16	All transplantations combined: • 72% at 1 y • 57% at 5 y	NR

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.
[a] Living donors.

Complications

Clouse (2019) reported on the incidence of graft-versus-host disease (GVHD) following intestine transplant at a single center.[13] Of the 236 transplants performed between 2003 and 2015, 37 patients (16%) developed GVHD. Mortality was 54% within one year of diagnosis for these patients. An increased risk of GVDH was seen with liver inclusion and increasing graft volume.

Spence (2020) published on the development of intra-abdominal infections within two years following intestinal and multivisceral transplants in adults at a single center.[14] There were 103 patients that were included, who underwent transplantations between 2003 and 2015, and 46 of these (43%) had intra-abdominal infections with the two-year follow-up. The median time to infection was 23 days post-transplant. Six patients also had concurrent blood stream infections. While patients with intra-abdominal infections had longer hospital stays than those without (median 35 days vs. 23 days, p=0.0012), there was no difference in all-cause mortality.

A report of thrombotic and hemorrhagic complications associated with visceral transplantation was published by Raveh (2018).[15] Data from 48 adult transplantations (32 multivisceral, 10 isolated intestinal, and six modified multivisceral) between 2010 and 2017 were reviewed retrospectively. There were eight patients who experience intraoperative intracardiac thrombosis (ICT)/pulmonary embolism (PE), all of whom were undergoing multivisceral transplants. Postoperative bleeding complications at one month were found in 11% of multivisceral transplants, 20% of isolated intestinal transplants, and 17% of modified multivisceral transplants.

Danziger-Isakov (2018) evaluated the epidemiology and outcomes of inpatient respiratory virus infection in pediatric patients following solid organ transplant at nine U.S. transplant centers.[16] Among the 42 patients who underwent intestine/multivisceral transplantation, respiratory virus infection occurred in 38%, the highest rate by transplant type. Respiratory virus infection was associated with younger age at transplant.

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Vo (2018) reported on the risk of invasive pneumococcal infections among pediatric patients receiving liver-small bowel-pancreas transplants at a single center.[17] Of the 122 patients who underwent this procedure between 2008 and 2016, nine patients experienced 12 invasive pneumococcal infections. The median time to first infection following transplant was three years (range 0.8 to 5.8 years), and the mortality rate was 22%. The authors noted that all patients were on prophylactic oral penicillin and the majority had received at least one dose of pneumococcal conjugate vaccine.

Nagai (2016) reported on cytomegalovirus (CMV) infection after intestinal or multivisceral transplantation at a single center in the US.[18] A total of 210 patients had in intestinal transplant, multivisceral transplant or modified multivisceral transplant between January 2003 and June 2014. The median length of follow-up was 2.1 years. A total of 34 patients (16%) developed CMV infection a median of 347 days after transplantation. Nineteen patients had tissue invasive CMV disease. CMV infection was significantly associated with rejection (odds ratio 2.6, $p<0.01$) and adversely affected patient survival (hazard ratio 2.7, $p<0.001$). A report from another center in the US, 16 of 85 (19%) patients undergoing intestinal or multivisceral transplantation developed CMV infection a mean of 139 days (range 14 to 243 days) postoperatively.[19]

Wu (2016) investigated the incidence and risk factors of acute antibody-mediated rejection (ABMR) among patients undergoing intestinal transplantation (n=175).[20] Acute ABMR was diagnosed by: clinical evidence; histologic evidence of tissue damage; focal or diffuse linear C4d deposition; and circulating anti-human leukocyte antigen antibodies. Of the 175 intestinal transplants, 58% were liver-free grafts, 36% included a liver graft, and 6.3% were retransplantations. Eighteen cases of acute ABMR were identified: 14 (14%) among the patients undergoing first liver-free transplantation, two (3%) among patients undergoing liver/small bowel transplantations, and two (18%) among the patients undergoing retransplantation. Graft failure occurred in 67% of patients with acute ABMR. The presence of a donor-specific antibody and a liver-free graft were associated with the development of acute ABMR.

In a case series by Cromvik (2016), five of 26 patients (19%) were diagnosed with GVHD after intestinal or multivisceral transplantation at a center in Sweden.[21] Risk factors for GVHD were malignancy as a cause of transplantation and neoadjuvant chemotherapy or brachytherapy before transplantation.

A 2015 retrospective review reported a number of parameters for intestinal and multivisceral transplants performed on Nordic patients between 1998 and 2013.[22] Twenty out of the 29 patients (69%) received liver-containing allografts. Nineteen of them were multivisceral grafts, including the stomach, the pancreaticoduodenal complex, the liver and the small intestine. The remaining liver-containing allograft was a combined liver and intestinal graft with a segmental pancreas. Three of eight patients with a spleen included in their multivisceral graft developed GVHD. One patient with GVHD and manifestations with skin rash later developed post-transplant lymphoproliferative disorder (PTLD).

A 2012 retrospective review focused on the rate of kidney dysfunction, a recognized complication after non-renal solid organ transplantation, in 33 multivisceral and 15 isolated small bowel transplant patients.[23] A significant decline in kidney function was reported in 46% of patients at one year following transplantation. A significant correlation was found for patient age, pretransplant serum creatinine, estimated GFR (eGFR) at post-transplant day 30, 90,

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180, and 270, and tacrolimus level at post-transplant day seven. Lesser decline was found in pediatric patients and patients with multivisceral transplantation compared with adults or isolated small bowel transplantation.

A 2012 retrospective review reported on bloodstream infections among 98 children younger than age 18 years with small bowel/combined organ transplants.[24] Seventy-seven (79%) patients underwent small bowel transplant in combination with a liver, kidney, or kidney-pancreas, and 21 had an isolated small bowel transplant. After a median follow-up of 52 months, 58 (59%) patients remained alive. The one-year survival rate was similar in patients with combined small bowel transplant (75%) and those with isolated small bowel transplant (81%). In the first year after transplantation, 68 patients (69.4%) experienced at least one episode of bloodstream infection. The one-year survival rate for patients with bloodstream infections was 72% compared to 87% in patients without bloodstream infections (p=0.056 for difference in survival in patients with and without bloodstream infections).

Wu (2011) reported on complications after small bowel and multivisceral transplantation in 241 patients who underwent intestinal transplantation.[25] Of these, 147 (61%) had multivisceral transplants, 65 (27%) had small bowel transplants and 12% had small bowel/liver transplants. There were 151 children (63%) and 90 adults. A total of 22 patients (9%) developed graft-versus-host disease (GVHD). Children younger than five years old were more likely to develop GVHD; the incidence in this age group was 16 of 121 (13.2%) compared to 2 of 30 (6.7%) in children between 5 and 18 years and 9 of 90 (4.4%) in adults over 18 years. Among diseases, patients with intestinal atresia were more likely to develop GVHD than those with other conditions (22.2% vs. 2.6%, respectively, p=0.03).

Transplant Recipients with Malignancies

Cruz (2011) published results from a small case series (n=10) of patients with intra-abdominal desmoid tumors secondary to familial adenomatous polyposis who underwent multivisceral transplant.[26] All patients were able to discontinue home parenteral nutrition by an average 30 days after transplant. Estimated survival was 80% at five years, and desmoid tumors reoccurred in one patient 15 months after transplantation. However, conclusions from this study are limited by the small sample size and the lack of a comparison group, factors which do not allow for the isolation of transplant as a causative factor in patient health outcomes.

HIV Positive Transplant Recipients

Solid organ transplant for patients who are HIV-positive was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. Currently, OPTN policy permits HIV-positive transplant candidates .[27]

Retransplantation

Evidence for the use of retransplantation to treat individuals who have failed intestinal transplantations includes several case series, mostly from single institutions. One case series analyzed records from the United Network for Organ Sharing database.[4] Among the case series described in Table 3, reasons for retransplantation include: acute rejection, chronic rejection, CMV, liver failure, lymphoproliferative disorder, and graft dysfunction. Survival rates for retransplantation are listed in Table 4.

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Table 3. Summary of Key Case Series Characteristics for Retransplantation[5]

Author (Year)	Location	N	Median Age (Range), y	Interventions		Follow-Up, (Range), mo
				Treatment	n	
Ekser (2018)[28]	United States	18	27 (0.9-57)	• Isolated IT • Modified MVT • Multivisceral graft	1 1 16	NR
Kubal (2018)[29]	United States	23	27 (1-58)	• Isolated IT • Multivisceral graft	1 22	NR
Lacaille (2017)[7]	France	10	13 (5-16)	• Isolated IT • Combined liver IT	3 7	4
Desai (2012)[4]	United States	• 72 (adults) • 77 (children)	NR	*Adults:* • Isolated IT • Combined liver IT *Children:* • Isolated IT • Combined liver IT	 41 31 28 49	NR
Abu-Elmagd (2009)[3]	United States	47	NR	• Isolated IT • Combined liver IT • Multivisceral graft	31 7 9	NR
Mazariegos (2008)[30]	United States	14	9.4 (3.2-22.7)	• Isolated IT • Combined liver IT • Multivisceral graft	1 3 10	55.9

IT: intestinal transplantation; NR: not reported.

Table 4. Summary of Key Case Series Results for Retransplantation[5]

Author (Year)	Interventions		Survival	Off TPN
	Treatment	n		
Ekser (2018)	• Isolated IT • Multivisceral graft • Modified multivisceral graft	1 1 16	Graft survival: • 71% at 1 y, 56% at 3 y, 44% at 5 y Patient survival: • 71% at 1 y, 47% at 3 y, 37% at 5 y	NR
Kubal (2018)[29]	• Isolated IT • Multivisceral graft	1 22	All transplantations combined: • 34% at 1 y	NR
Lacaille (2017)[7]	• Isolated IT • Combined liver IT	3 7	All transplantations combined: • 30% at last follow-up	NR
Desai (2012)[4]	*Adults:* • Isolated IT • Combined liver IT *Children:* • Isolated IT • Combined liver IT	 41 31 28 49	*Adults:* • 80% at 1 y; 47% at 3 y; 29% at 5 y • 63% at 1 y; 56% at 3 y; 47% at 5 y *Children:* • 81% at 1 y; 74% at 3 y; 57% at 5 y • 42% at 1 y; 42% at 3 y; 42% at 5 y	NR
Abu-Elmagdl (2009)[3]	• Isolated IT • Combined liver IT • Multivisceral graft	31 7 9	All transplantations combined: • 69% at 1 y • 47% at 5 y	NR
Mazariegos (2008)[30]	• Isolated IT • Combined liver IT • Multivisceral graft	1 3 10	All transplantations combined: • 71% at last follow-up	100%

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IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2003, the American Gastroenterological Association published a position statement on short bowel syndrome and intestinal transplantation.[31] The statement noted that only patients with life-threatening complications due to intestinal failure or long-term total parenteral nutrition have undergone intestinal transplantation. The statement recommended the following Medicare-approved indications, pending availability of additional data:

- Impending liver failure
- Thrombosis of major central venous channels
- Frequent central line associated sepsis
- Frequent severe dehydration.

SUMMARY

There is enough research to show that small bowel/liver and multivisceral transplant and retransplant can improve survival in certain patients. Therefore, these procedures may be considered medically necessary for patients with intestinal failure who have been managed with long-term total parenteral nutrition and who have developed evidence of impending end-stage liver failure. Transplants or retransplants are considered not medically necessary when the policy criteria are not met.

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CODES

Codes	Number	Description
CPT	43999	Unlisted procedure, stomach
	44132	Donor enterectomy, (including cold preservation) open; from cadaver donor
	44133	Donor enterectomy, (including cold preservation) open; partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each

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Codes	Number	Description
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
	44799	Unlisted procedure, small intestine
	47133	Donor hepatectomy, (including cold preservation) from cadaver donor
	47135	Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age
	47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
	47141	;total left lobectomy (segments II, III and IV)
	47142	;total right lobectomy (segments V, VI, VII and VIII)
	47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
	47144	;with trisegment split of whole liver graft into 2 partial liver grafts (ie, left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
	47145	;with lobe split of whole liver graft into 2 partial liver grafts (ie, left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
	47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
	47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each
	47399	Unlisted procedure, liver
	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
	48999	Unlisted procedure, pancreas
HCPCS	S2053	Transplantation of small intestine, and liver allografts
	S2054	Transplantation of multivisceral organs
	S2055	Harvesting of donor multivisceral organs, with preparation and maintenance of allografts; from cadaver donor
	S2152	Solid organs(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre and posttransplant care in the global definition

Date of Origin: *January 1996*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.22

Hematopoietic Cell Transplantation for Multiple Myeloma and POEMS Syndrome

Effective: December 1, 2019

Next Review: August 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic cell transplant may be considered **medically necessary** to treat multiple myeloma or POEMS syndrome for either of the following (A. or B.):
   A. Single initial or second (salvage) transplant to treat multiple myeloma.
   B. Patients with disseminated POEMS syndrome. Patients with disseminated POEMS syndrome may have diffuse sclerotic lesions or disseminated bone marrow involvement.

II. Tandem hematopoietic cell transplant may be considered **medically necessary** to treat newly diagnosed (i.e., previously untreated) multiple myeloma for either of the following (A. or B.):
   A. Autologous-autologous tandem hematopoietic cell transplant

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B. Tandem transplantation with an initial autologous hematopoietic cell transplant followed by reduced-intensity conditioning allogeneic hematopoietic cell transplant

III. Hematopoietic cell transplant is considered **investigational** in the treatment of multiple myeloma or POEMS syndrome for any of the following (A.-D.):

A. Tandem hematopoietic cell transplant for POEMS syndrome

B. Myeloablative allogeneic hematopoietic cell transplant as initial therapy for newly diagnosed (i.e., previously untreated) multiple myeloma or as salvage therapy (after a failed prior course of autologous hematopoietic cell transplant)

C. Nonmyeloablative (reduced intensity conditioning) allogeneic hematopoietic cell transplant as an initial therapy for newly diagnosed (i.e., previously untreated) multiple myeloma or as salvage therapy (after a failed prior course of autologous hematopoietic cell transplant)

D. Allogeneic hematopoietic cell transplant to treat POEMS syndrome

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant, including specific type of transplant being requested (single initial or second [salvage] autologous transplant vs. tandem hematopoietic cell transplant)

CROSS REFERENCES

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1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the

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patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the condition with lower doses or less-intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

MULTIPLE MYELOMA (MM)

Multiple myeloma is a systemic malignancy of plasma cells that represents a small but significant proportion of all hematologic cancers. It is treatable but rarely curable, with estimated new cases and deaths in 2017 in the U.S. of 30,280 and 12,590, respectively.[1] At the time of diagnosis most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease.

The disease is staged by estimating tumor mass, based on various clinical parameters like hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure.[1] Multiple myeloma usually evolves from an asymptomatic premalignant stage (termed "monoclonal gammopathy of undetermined significance" or MGUS). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic multiple myeloma prolongs survival when compared to therapy delivered at the time of symptoms or end-organ damage.[1,2] In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized, and referred to as smoldering multiple myeloma.[3] The overall risk of disease progression from smoldering to symptomatic multiple myeloma is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 years.[2]

POEMS SYNDROME

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia.[4,5] This complex, multiorgan disease was first described in 1938, but the acronym –

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POEMS - was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.[6] No single test establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence suggests it is mediated by imbalance of proinflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved.[5,7] However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in the table below. Both major criteria and at least one of the minor criteria are necessary for diagnosis.[7]

Criteria for the Diagnosis of POEMS Syndrome[5,7]

Major Criteria	Minor Criteria	Known Associations	Possible Associations
• Polyneuropathy • Monoclonal plasma-proliferation disorder	• Sclerotic bone lesions • Castleman disease • Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Edema (edema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails) • Papilledema	• Clubbing • Weight loss • Thrombocytosis • Polycythemia • Hyperhidrosis	• Pulmonary hypertension • Restrictive lung disease • Thrombotic diatheses • Arthralgias • Cardiomyopathy (systolic dysfunction) • Fever • Low vitamin B12 values • Diarrhea

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.[8] Other large series have been described in the United States[5,7,9] and in India.[10] In general, patients with POEMS have a superior overall survival compared with that of multiple myeloma; with one study reporting a median survival of nearly 14 years, in a large series from the Mayo Clinic.[7] However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported.[11] Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HCT support.[5,7] Optimal treatment involves eliminating the plasma cell clone, for example by surgical excision or local radiation therapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.[5,12]

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time

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following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of multiple myeloma or POEMS syndrome, comparative clinical trials that compare this therapy to standard medical treatment, such as standard conditioning regimens, are needed. Further, for treatment of hematologic malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

SINGLE AUTOLOGOUS HCT

As a result of several prospective, randomized trials that were conducted comparing conventional chemotherapy with high-dose therapy and autologous HCT for patients with multiple myeloma, autologous HCT has become the treatment of choice in patients younger than 65 years of age.

Systematic Reviews

A meta-analysis of 2,411 patients enrolled in randomized controlled trials compared standard dose chemotherapy versus myeloablative chemotherapy with single autologous hematopoietic stem cell transplant (HCT).[13] The authors of the meta-analysis concluded that myeloablative therapy with autologous HCT increased the likelihood of PFS (hazard of progression=0.75; 95% CI: 0.59–0.96) but not OS (hazard of death=0.92; 95% CI: 0.74–1.13); the odds ratio for treatment-related mortality was 3.01 (95% CI: 1.64–5.50) in the group with autologous HCT. However, the effects of myeloablative chemotherapy and autologous HCT may have been diluted by the fact that up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HCT as salvage therapy when the multiple myeloma progressed. This could account for the lack of a significant difference in OS between the two groups in the study.

Randomized Controlled Trials

In a randomized, open label phase 3 trial from the Intergroupe Francophone Myelome (IFM)/Dana-Farber Cancer Institute (DFCI), Attal (2017) compared consolidation therapy using five cycles of combination chemotherapy to HCT followed by two cycles of combination chemotherapy.[14] Seven hundred patients with symptomatic, measurable, newly diagnosed multiple myeloma were randomized to one of two treatment arms. All patients received induction therapy with three cycles of lenalidomide, bortezomib, and dexamethasone (RVD). As consolidation therapy, the transplant arm received high-dose melphalan and stem-cell transplantation followed by two cycles of RVD, whereas the chemotherapy arm received five additional cycles of RVD.

The primary end point was progression-free survival. Response rate, time to disease progression, overall survival, and adverse event rates were reported as secondary end points. A statistically significant difference between groups was reported for median progression-free survival, which was longer in the transplantation group than the chemotherapy-only group (50 and 36 months, respectively; adjusted hazard ratio for disease progression or death, 0.65; $p<0.001$). The benefit was found to apply to all patient subgroups tested. The difference in complete response rates was statistically significant, with a rate of 48% in the chemotherapy-

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alone group and 59% in the transplantation group (p=0.03). Overall survival was not significantly different at four years between the transplantation group and the chemotherapy-only group (81 and 82%, respectively). The transplantation group had significantly higher rate of grade 3 or 4 neutropenia (92%), rate of grade 3 or 4 gastrointestinal disorders (28%), and rate of infections (20%) than the chemotherapy only group (47, 7, and 9%, respectively).

Gay (2015) compared autologous HCT to standard chemotherapy plus lenalidomide, a newer agent for treatment of MM.[15] The study was an open label RCT from 59 centers in Europe and Australia that used a 2x2 factorial design to compare four groups 1) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide alone, 2) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide and prednisone 3) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide alone, and 4) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide plus prednisone. The primary outcome for this study was progression-free survival. (PFS), and mean followup at the time of publication was 52 months. Median PFS was superior for the HCT group compared to chemotherapy plus lenalidomide (43.3 months, 95% CI 33.2-52.2months vs 28.6 months, 95% CI 20.6-36.7mths, p<0.0001). The rate of grade 3 or 4 adverse events was higher for the HCT group compared to chemotherapy for hematological events (84% vs 26%), gastrointestinal complications (20% vs 5%), and infections (19% vs 5%).

Data are available from seven randomized trials of autologous HCT following induction therapy that were designed and implemented prior to the availability of thalidomide, lenalidomide, and bortezomib.[16-22] The introduction of these agents has dramatically changed the treatment paradigm of multiple myeloma. Trials incorporating these newer agents into induction regimens are ongoing. Preliminary results have shown CRs in a substantial proportion of these patients, opening the question as to what role autologous HCT will continue to play a role. However, it will require further follow-up to determine if these newer induction regimens will translate into improved survival.[23]

In all but one (Barlogie, 2006) of the seven studies, the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HCT arm.[21] This study published final results of the S9321 trial, which was initiated in 1993, and randomized 516 patients with multiple myeloma to receive either standard therapy or myeloablative conditioning with melphalan 140 mg/m^2 plus total body irradiation followed by autologous HCT.[21] The authors reported virtually no difference in outcomes, including response rates, progression-free survival, and OS. In five of the seven studies, the superior CR rate translated into a significant increase in progression-free survival (PFS). However, in the two studies that did not show an improved PFS with autologous HCT, randomization was not performed at diagnosis, but only after induction treatment, possibly introducing selection bias.[22] Three of the seven studies showed superior OS in the autologous HCT group.[16,17,19] The Intergroupe Francophone du Myélome (IFM) showed the superiority of high-dose chemotherapy and autologous HCT compared to conventional chemotherapy in a randomized trial of 200 patients younger than 65 years of age.[16] The group that underwent autologous HCT had significantly improved response rates, event-free and overall survival. Seven years later, the British Medical Research Council published similar results.[17]

The reasons for the discrepant results among these randomized studies are uncertain, but may be related to the conditioning regimens or patient age.

SALVAGE TRANSPLANTATION

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Despite the success in improved survival with autologous HCT versus conventional chemotherapy, nearly all patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed multiple myeloma after a prior autologous HCT include novel biologic agents (e.g., thalidomide, lenalidomide and bortezomib, as single agents, in combination with dexamethasone, and in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HCT. No clear standard of care exists.

Repeat Autologous HCT for Relapse after Initial Autologous HCT

Systematic Reviews

An evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from 4 relevant clinical series.[24] Investigators reported that some myeloma patients who relapsed after a first autotransplant achieved durable complete or partial remissions after a second autotransplant as salvage therapy. Factors that apparently increased the likelihood of durable remissions and extended survival included a chemosensitive relapse, younger age, a long disease-free or progression-free interval since the initial autotransplant, and fewer chemotherapy regimens prior to the initial autotransplant. Thus, clinical judgment plays an important role in selecting patients for this treatment with a reasonable likelihood that potential benefits may exceed harms.

Randomized Controlled Trials

In 2014, Cook published a multicenter, randomized, open-label, phase 3 study from 51 centers across the United Kingdom, that included patients aged at least 18 years with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT.[25] Before randomization, eligible patients received bortezomib, doxorubicin, and dexamethasone (PAD) induction therapy and then underwent peripheral blood stem cell mobilization and harvesting, if applicable. Eligible patients were randomly assigned (1:1) to receive either high-dose melphalan 200 mg/m2 plus salvage autologous HCT or oral cyclophosphamide (400 mg/m2/wk for 12 weeks). The primary end point was time to disease progression, analyzed by intention to treat. A total of 297 patients were enrolled, of whom 293 received PAD reinduction therapy. Among the latter, 174 patients with sufficient harvest of peripheral blood stem cells were randomly allocated to undergo salvage HCT (n=89) or receive cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HCT group than in the cyclophosphamide group (19 months [95% CI, 16 to 25] vs 11 months [95% CI, 9 to 12]; hazard ratio=0.36 [95% CI, 0.25 to 0.53]; p<0.001). Frequently reported (>10% of patients) grade 3-4 morbidity with PAD induction, salvage HCT, and cyclophosphamide were: neutropenia (125 [43%] of 293 patients after PAD and 63 [76%] of 83 patients in the salvage HCT group vs 11 [13%] of 84 patients in the cyclophosphamide group), thrombocytopenia (150 [51%] after PAD, and 60 [72%] vs four [5%], respectively), and peripheral neuropathy (35 [12%] after PAD, and none vs none, respectively). This study provides additional evidence for a net benefit of high-dose melphalan plus salvage HCT when compared with cyclophosphamide in patients with relapsed MM eligible for intensive therapy.

Final survival data for the trial was reported in 2016.[26] The HCT group had superior overall median survival compared to the chemotherapy group (67 months, 95% CI 55mths-not estimable vs 52 months, 95% CI 42-60mths, p<0.0001). Time to disease progression continued to favor the HCT group at the longer followup (19 months, 95% CI 16-26mths vs 11 months, 95% CI 9-12mths, p=0.02). There were no further adverse events related to the HCT

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procedure reported during longer followup. The cumulative incidence of second malignancies was 5.2% (95% CI 2.1-8.2%).

Nonrandomized Studies

Olin reported their experience with 41 patients with multiple myeloma who received a second salvage autologous HCT for relapsed disease.[27] Median time between transplants was 37 months (range 3–91 months). Overall response rate in assessable patients was 55%. Treatment-related mortality was 7%. Median follow-up time was 15 months, with median PFS of 8.5 months and median OS 20.7 months. In a multivariate analysis of OS, the number of prior lines of therapy (≥5) and time to progression after initial transplant were the strongest predictors of OS.

Although not conclusive, available evidence on the use of autologous transplant following relapse is sufficient to suggest treatment benefit.

Allogeneic HCT for Relapse after Initial Autologous HCT

Nonrandomized Studies

Schneidawind (2017) reported on consecutive patients (N=41) who received an allogeneic HCT for the treatment of relapsed or refractory multiple myeloma from 2001 to 2015. Ninety five percent of patients had previously received autologous HCT (18 tandem; 21 single high-dose chemotherapy followed by autologous HCT). Allogeneic HCT following the single approach was associated with an increased 3-year EFS (24% vs 6%, P=0.04) and OS (64% vs 35%, P=0.09) compared with a tandem autologous approach. Additionally, allogeneic HCT following the tandem autologous approach was associated with an increased relapse/progression rate (72% vs 58%, P=0.30).

Qazilbash reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant.[28] Fourteen patients (median age: 52 years) received a second autologous transplant and 26 patients (median age: 51 years) underwent a reduced-intensity allogeneic transplant. Median interval between first and second transplant was 25 and 17 months for the autologous and allogeneic groups, respectively. After a median follow-up of 18 months (range: 2–69 months) for the autologous group, median PFS was 6.8 months and OS 29 months. After a median follow-up of 30 months (range: 13–66 months) for the allogeneic group, median PFS was 7.3 months and OS 13 months. On univariate analysis, in the allogeneic group, an interval of greater than 1 year between the first and salvage transplants predicted a significantly better OS (p=0.02). None of the prognostic factors that were evaluated for the allogeneic group was found to have a significant impact on survival in the autologous group (which included age, cytogenetics, type of donor, and chronic graft-versus-host disease [GVHD], among others).

The European Group for Blood and Marrow Transplant (EBMT) reported an analysis of 413 patients who received a related or unrelated RIC allogeneic HCT for the treatment of relapse or disease progression after a prior autologous HCT.[29] Median age at RIC allogeneic HCT was 54 years, and 45% of patients had undergone two or more prior autologous transplants. The median OS and PFS from the time of allogeneic transplantation for the entire population were about 25 and 10 months, respectively. Cumulative non-relapse mortality (NRM) at 1 year was about 22%. In a multivariate analysis, cytomegalovirus (CMV) seronegativity of both patient and donor was associated with significantly better PFS, OS and NRM. Patient-donor

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gender mismatch was associated with better PFS. Fewer than two prior autologous transplants was associated with better OS and shorter time from the first autologous HCT to the RIC allogeneic HCT was associated with lower NRM. Findings suggested patient and donor CMV seronegativity may represent key prognostic factors for outcome after RIC allogeneic HCT in cases of relapse or progression following one or more autologous transplants.

Evidence on the use of allogeneic transplant as salvage treatment after initial autotransplant is not suggestive of increased treatment benefit compared with autologous transplant.

TANDEM TRANSPLANT

A tandem transplant involves an autologous transplant followed by a preplanned second transplant, either another autologous or a reduced-intensity conditioning (RIC) allogeneic transplant. A tandem transplant differs from a second, salvage transplant in that a tandem transplant involves prospective planning for a second transplant at the time the first transplant is being planned.

Tandem Autologous-Autologous HCT

Randomized Controlled Trials

The Bologna 96 clinical study (2007), compared single with double autologous HCT (n=321).[30] Patients undergoing tandem autologous HCT were more likely than those with a single autologous HCT to attain at least a near complete response (47% vs. 33%; p=0.008), to prolong relapse-free survival (median, 42 vs. 24 months; p<0.001), and extend event-free survival (median, 35 vs. 23 months; p=0.001). There was no significant difference between the groups in treatment-related mortality (3–4%). There was a trend for improved OS among patients in the double-transplantation group (7-year rate of 60%) as compared with the single-transplantation group (7-year rate of 47%; p=0.10). Conversely, among patients achieving CR or near CR after one transplant, EFS and OS were not significantly different according to transplantation(s) received by study randomization. A subgroup analysis of outcomes of patients assigned to the two treatment arms was evaluated according to response, and showed similar results to the Attal study (described below), in that the benefit of a second transplant was seen only in patients that did not achieve at least a very good partial response with the first transplant.[31] However, the methodological shortcomings limit reliability of this finding.

The first randomized trial of autologous tandem transplants (IFM-94) was published in December 2003 by Attal and randomized patients with newly diagnosed (i.e., previously untreated) myeloma to single or tandem autologous transplants.[31] Outcomes were analyzed by intention-to-treat at 75 months' median follow-up. Among those randomized to single transplants (n=199), 148 relapsed: 33 were salvaged with a second autotransplant, 13 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Among those randomized to tandem autotransplants (n=200), 129 patients experienced disease relapse: 34 received salvage therapy with another (3rd) transplant, 12 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Seven years after diagnosis, patients randomized to tandem transplants had higher probabilities than those randomized to single transplants for event-free (EFS; 20% vs. 10%, p=0.03), relapse-free (RFS; 23% vs. 13%; p<0.01), and overall (OS; 42% vs. 21%, p=0.010) survival. Treatment-related mortality was 6% and 4% after tandem and single transplants, respectively (p=0.40). Second transplants apparently extended survival only for those who failed to achieve

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a complete (CR) or very good partial response (VGPR) after one transplant (OS at 7 years: 43% vs. 11%, p<0.001), however the methodological shortcomings limit reliability of this finding (comparing outcomes in subgroups was not one of the study objectives, study was not adequately powered for subgroup analyses).

An accompanying editorial by Stadtmauer raised concerns that these results might be specific to the regimens used for myeloablative therapy in IFM-94.[32] Patients in the single transplant arm received 140 mg/m^2 melphalan plus total-body irradiation (TBI), while those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. The editorial cites an IFM-95 study as evidence, suggesting 140 mg/m^2 melphalan plus TBI may be less effective and more toxic than myeloablative therapy than 200 mg/m^2 melphalan and no TBI. Based on this, the author hypothesizes increased survival in the IFM-94 tandem arm may have resulted from greater cumulative exposure to melphalan (280 vs. 140 mg/m2).

Results from available RCTs demonstrated small but significant clinical improvements with tandem autologous transplants among treatment naïve patients; such evidence may be suggestive of a treatment benefit. However, methodological limitations demonstrate the need for additional clinical trials.

Tandem Autologous/Reduced-Intensity Conditioning (RIC) Allogeneic HCT

Several randomized controlled trials have been published comparing RIC-allogeneic HCT following a first autologous HCT to autologous transplants, single or in tandem. These studies were based on “genetic randomization,” that is, patients with an HLA-identical sibling were offered an RIC-allogeneic HCT following the autologous HCT, whereas the other patients underwent either one or two autologous transplants.

Maffini (2018) published long-term follow-up results for multiple myeloma patients treated with tandem autologous-allogeneic HCT.[33] The study consisted of 209 patients (86%) who received tandem HCT upfront and 35 patients (14%) who received tandem HCT after failing a previous autologous HCT. Median follow-up was 8.3 years. Five-year overall survival (OS) and progression-free survival (PFS) were 54% (95% CI: 48-60%) and 31% (95% CI: 25-36%), respectively; 10-year OS and PFS were 41% (95% CI: 34-48%) and 19% (95% CI: 13-24%), respectively. Overall non-relapse mortality was 2% at 100 days and 14% at 5 years.

Krishnan conducted a Phase 3 trial, published in 2011, comparing tandem autologous-autologous HCT (auto-auto group) versus tandem autologous-RIC allogeneic HCT (auto-allo group) in patients from 37 transplant centers in the U.S., who between 2003 and 2007, had received an autologous HCT (n=710).[34] Of these patients, 625 had standard-risk disease and 156 of 189 patients (83%) in the auto-allo group and 366 of 436 (84%) in the auto-auto group received a second transplant. Patients were eligible if they were younger than 70 years of age and had completed at least three cycles of systemic therapy for myeloma within the past 10 months. Patients were assigned to receive a second autologous or allogeneic HCT based on the availability of an HLA-matched sibling donor. Patients in the auto-auto group subsequently underwent random assignment to observation (n=219) or maintenance therapy with thalidomide plus dexamethasone (n=217). Kaplan-Meier estimates of three-year PFS were 43% (95% CI: 36-51) in the auto-allo group and 46% (42-51) in the auto-auto group (p=0.67). OS also did not differ at three years (77% [95%CI 72-84] versus 80% [77-84]; p=0.19). Grade 3-5 adverse events between the two groups were 46% and 42%, respectively. The authors

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concluded that non-myeloablative allogeneic HCT after autologous HCT is not more effective than tandem autologous HCT for patients with standard-risk myeloma.

Rosinol (2008) reported the results of a prospective study of 110 patients with multiple myeloma who failed to achieve at least near-complete remission after a first autologous HCT and were scheduled to receive a second autologous transplant (n=85) or an RIC-allogeneic transplant (n=25), depending on the availability of an HLA-identical sibling donor.[35] The autologous/RIC-allogeneic group had a higher CR rate (40% vs. 11%; p=0.001) and a trend toward a longer PFS (median 31 months vs. not reached, p=0.08). There was no statistical difference in EFS or OS between the two groups. The autologous/RIC-allogeneic group experienced a higher transplantation-related mortality rate (16% vs. 5%; p=0.07) and a 66% chance of chronic graft-versus-host disease.

One study by Bruno (2007) included 80 patients with an HLA-identical sibling and who were allowed to choose allografts or autografts for the second transplant (58 completed an autograft/allograft sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence).[36] The results among those completing tandem transplantation showed a higher complete response rate at the completion of the second transplant for the autograft/allograft group (55%) than for the autograft/autograft group (26%; p=0.004). EFS and OS were superior for the patients who underwent autologous-allogeneic transplantation (35 months vs. 29; p=0.02 and 80 months vs. 54; p=0.01, respectively). Analyzing the group with HLA-identical siblings versus those without, in a pseudo intention-to-treat analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The treatment-related mortality rate at two years was 2% in the double autograft group and 10% in the autograft/allograft group; 32% of the latter group had extensive, chronic graft-versus-host disease.

The first published study by Garban (2006) included high-risk patients (including deletion of chromosome 13).[37] Sixty-five patients were in the autologous/RIC-allogeneic group and 219 in the autologous/autologous group. Based on the intention-to-treat analysis, there was better median EFS and OS in the autologous/autologous group (35 months versus 31.7; p=NS and 47.2 months versus 35; p=0.07, respectively). If results for only those patients who actually received the autologous/RIC-allogeneic (n=46) or tandem autologous transplants (n=166) were analyzed, the superior OS was again seen in the tandem autologous group (median 47.2 vs. 35 months; p=0.07). Updated results of this population were reported with a reference date of July 2008 by Moreau[38] Comparing the results of the 166 patients who completed the whole tandem autologous HCT protocol to the 46 patients who underwent the entire autologous/RIC-allogeneic program, no difference was seen regarding EFS (median 25 vs. 21 months, p=0.88), with a trend toward superior OS in favor of double autologous HCT (median OS 57 vs. 41 months; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

Although the results differ among the Garban/Moreau study[37,38] and the other studies[34-36] the authors of the Moreau study suggested that this is due to different study designs. The Moreau study update focused on patients with high-risk disease and involved a conditioning regimen before the RIC-allogeneic transplant that may have eliminated some of the graft-versus-myeloma effect. Other contributing factors may have been non-uniform preparative regimens, different patient characteristics and criteria for advancing to a second transplant (i.e., only patients who failed to achieve a CR or near CR after the first autologous transplant underwent a second), and a small population in the allogeneic group in the Moreau study. The authors

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suggest that the subgroup of high-risk patients with de novo multiple myeloma may get equivalent or superior results with a tandem autologous/autologous transplant versus a tandem autologous/RIC-allogeneic transplant, and that in patients with standard-risk and/or chemosensitive multiple myeloma, RIC allograft may be an option.

Interim Study Findings

Currently, the final results of two recently completed prospective Phase III trials comparing double autologous with single autologous followed by RIC-allogeneic transplant are awaited.[39,40] Interim results of the study by the HOVON Group at 36 months of follow-up found no significant difference between the groups that received autologous/RIC-allogeneic transplants or tandem autologous transplants in EFS (median 34 months and 28 months, respectively) or OS (80% and 75%, respectively) at 36 months.[39]

An interim analysis of a European Group for Blood and Marrow Transplant (EBMT) study was recently presented with somewhat different inclusion criteria.[40] Previously untreated patients received vincristine, doxorubicin, dexamethasone (VAD) or VAD-like induction treatment, and had a response status of at least stable disease (i.e., complete or partial remission or stable disease) at the time of autologous transplantation, which was also the time point for study inclusion. Patients with an HLA-identical sibling proceeded to RIC-allogeneic transplantation, while those without a matched sibling received no further treatment or a second autologous stem-cell transplant (if treated within a tandem program). A total of 356 patients were included, with a median follow-up of 3.5 years. Of these, 108 patients were allocated to the RIC-allogeneic transplant group and 248 to the autologous transplant group. Of the patients allocated to the allogeneic group, 98 received a RIC-allogeneic transplant. As of now, there is no significant difference in PFS or OS between the double autologous and autologous/RIC-allogeneic transplant recipients. However, the follow-up is too short for firm conclusions to be drawn and the study is still ongoing.

At 96 months in the EBMT trial, progression-free survival (PFS) and overall survival (OS) were 22% and 49% versus 12% (P = .027) and 36% (P = .030) with autologous/RIC-allogeneic (auto/RICallo) and autologous HCT, respectively.[41] The corresponding relapse/progression rate (RL) was 60% versus 82% (P = .0002) and the non-relapse mortality at 36 months was 13% versus 3% (P = .0004) with auto/RICallo and autologous HCT respectively. In patients with the del(13) abnormality corresponding PFS and OS were 21% and 47% in the auto/RICallo group versus 5% (P = .026), and 31% (P = .154) in the autologous only group. Long-term outcome in patients with multiple myeloma was better with auto/RICallo HCT as compared with autologous only and the auto/RICallo approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation. Authors called for longer follow-up periods of at least five years in order to better characterize the role of auto/RICallo HCT in patients with multiple myeloma.

ALLOGENEIC HCT

Even though myeloablative allogeneic HCT may be the only curative treatment in multiple myeloma (due to its graft-versus-myeloma effect), its use has been limited to younger patients. Even with the limited indications, the toxic death rate related to infections and GVHD is considered too high and this strategy has been almost completely abandoned.[42]

Mortality can be reduced through the use of RIC regimens, and can be considered for older patients up to 65 years of age. However, when RIC-allogeneic transplant is used in patients

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with a high tumor burden or with chemotherapy-resistant disease, the immunologic effect of the graft is not sufficient to avoid relapses.[42] Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HCT.[42]

The role of allogeneic HCT remains controversial, in particular because of conflicting data from cooperative group trials, but also because of confounding factors which may have influenced positive outcomes such as those observed with proteasome inhibitors, new immune modulatory agents, and the use of post-transplant maintenance therapy.[43,44] Overall the evidence on the use of allogeneic HCT as a first-line or salvage therapy does not suggest that potential treatment benefit outweighs risk of harm.

POEMS SYNDROME

Systematic Reviews

In 2012, Kuwabara performed a Cochrane review of HCT treatment of POEMS syndrome which identified no randomized controlled trials (RCTs), no quasi- RCTs, no historically controlled trials or trials with concurrent controls that met their study selection criteria.[11] The authors included 6 small series of patients (total n=57) who underwent autologous HCT. Two-year survival rates ranged from 94-100%. The review authors indicated that if all published experience with autologous HCT was pooled, transplant-related mortality would be 3 of 112 (2.7%). They caution that long-term outcomes with autologous HCT have not been elucidated and require continuing study.

A second 2012 review article indicated case series suggest most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m2.[5] Responses have been reported as durable but relapse occurs. Symptomatic progression has typically been reported as rare, with most progressions identified as rising vascular endothelial growth factor (VEGF) and radiographic. This author also reports that long-term outcomes with autologous HCT are unclear given the sparse numbers. However, a single-center series published in 2012 from Mayo Clinic reported a five-year OS of 94% and a PFS of 75% among 59 patients entered between 1999 and late 2011.[45]

It is unlikely that randomized controlled trials of HCT in patients with POEMS syndrome will be feasible, given the rarity of the condition. The current evidence regarding HCT in patients with POEMS Syndrome consists mainly of small case series[9,46-53] (n<60) and review articles.[54-57] In addition, the criteria for diagnosing and treating the multiple potential symptoms associated with POEMS, has not been well defined. However, for autologous HCT, a chain of indirect evidence suggests improved health outcomes, as several case studies have reported good clinical responses in patients diagnosed with POEMS syndrome. Without larger treatment studies, the efficacy of allogenic and tandem HCT for patients with POEMS is unknown.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

**All recommendations are category 2A unless otherwise noted. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.*

The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (MM) address the following:[58]

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Autologous Transplant

For active (symptomatic) myeloma "category 1 evidence supports proceeding straight after induction therapy to high-dose therapy and stem cell transplant" Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Additional treatment post-autologous cell transplant may include additional autologous cell transplant. "Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression. Retrospective studies suggest a 2- to 3-year minimum length of remission for consideration of a second autologous stem cell transplant for salvage therapy."

Tandem Transplant

"…a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT."

Allogeneic Transplant

For active (symptomatic) myeloma, the recommendation states: "Allogeneic stem cell transplant in multiple myeloma should only be used in the setting of a clinical trial. Current data do not support miniallografting alone."

The same recommendation is applied to post-autologous cell transplant scenarios for progressive disease and response or stable disease. For patients treated with or without a prior transplant, allogeneic cell transplant is also a recommended option for transplant candidates with relapse or progressive disease.

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published evidence-based guidelines for the use of HCT in patients with MM.[59] The guidelines are generally consistent with the conclusions in the above review of the literature. ASBMT recognizes that much of the RCT evidence summarized in the 2015 guidelines comes from trials that predate the advent of novel triple therapy induction regimens. Furthermore, advances in supportive care and earlier disease detection has increasingly influenced decision making and allows individual tailoring of therapy.

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION, EUROPEAN SOCIETY OF BLOOD AND MARROW TRANSPLANTATION, BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK, AND INTERNATIONAL MYELOMA WORKING GROUP

Following a 2014 meeting of multiple myeloma experts representing the above four groups, consensus guidelines were published regarding salvage autologous HCT, and the role of allogeneic HCT in relapsed myeloma.[60] Among the recommendations, the authors conclude that well-designed prospective trials are necessary to extensively explore therapy in the salvage setting. While the guidelines state that both autologous and allogeneic HCT should be considered as a clinical option, this is based on a Likert survey of agreement, and the role of allografting for relapsing after autologous HCT had much less consensus than the autologous setting.

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SUMMARY

MULTIPLE MYELOMA

There is enough research to show single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants for those with multiple myeloma may improve overall health outcomes. Outcomes include, but are not limited to, partial or complete response rates and prolongation of progression-free and overall survival. Practice guidelines based on research have specific recommendations for these regimes in specific patient populations. Therefore, single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants may be considered medically necessary in select patients when policy criteria are met.

There is not enough research to know if allogeneic hematopoietic cell transplant (including allo-HCT with myeloablative conditioning) improves overall health outcomes for those with multiple myeloma. Additionally, there is not enough research to know if single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants improves overall health outcomes when policy criteria are not met. Therefore, these treatment regimes are considered investigational unless policy criteria are met.

POEMS SYNDROME

There is enough research to show that overall survival may be improved with autologous hematopoietic cell transplant for those with disseminated POEMS syndrome. Therefore, this treatment may be considered medically necessary. Due to a lack of evidence, and practice guidelines, allogeneic and tandem hematopoietic cell transplant are considered investigational to treat POEMS syndrome when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic

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	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.23

Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphomas

Effective: December 1, 2019

Next Review: September 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Notes:

- Hematopoietic cell transplantation (HCT) in the treatment of Hodgkin's lymphoma is addressed in medical policy Transplant No. 45.30.
- HCT in the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma are considered separately in medical policy Transplant No. 45.35
- HCT in the treatment of Waldenstrom macroglobulinemia, a lymphoplasmacytic lymphoma, is considered separately in medical policy Transplant No. 45.40

I. Autologous hematopoietic cell transplantation may be considered **medically necessary** for treatment of non-Hodgkin's lymphomas except as an initial treatment for NHL.

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II. Autologous hematopoietic cell transplantation is considered **investigational** as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for non-Hodgkin's lymphomas.

III. Reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation may be considered **medically necessary** for treatment of non-Hodgkin's lymphomas when all of the following criteria are met (see Policy Guidelines):

   A. All of the medical necessity criteria for myeloablative allogeneic hematopoietic cell transplantation are met; and

   B. The patient does not qualify for a myeloablative allogeneic hematopoietic cell transplantation (see Policy Guidelines).

IV. Myeloablative allogeneic hematopoietic cell transplantation may be considered **medically necessary** for treatment of non-Hodgkin's lymphomas except as an initial treatment.

V. Myeloablative allogeneic hematopoietic cell transplantation is considered **investigational** as an initial treatment (i.e., without a full course of standard-dose induction chemotherapy) for non-Hodgkin's lymphomas.

VI. Tandem hematopoietic cell transplantation (e.g., autologous - autologous, autologous - allogeneic) is considered **investigational** to treat patients with any stage, grade, or subtype of non-Hodgkin's lymphomas.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

REDUCED-INTENSITY CONDITIONING

Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic stem-cell transplant (SCT) but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, or prior intensive chemotherapy) preclude use of a standard conditioning regimen.

In patients who qualify for a myeloablative allogeneic hematopoietic HCT on the basis of overall health and disease status, allogeneic HCT using either myeloablative or RIC may be

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considered. However, a myeloablative conditioning regimen with allogeneic HCT may benefit younger patients with good performance status and minimal comorbidities more than allogeneic HCT with RIC.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant
- Documentation of Relapse Risk Prognostic Factors
- For patients with a reduced-intensity conditioning (RIC) regimen, documentation supporting reasons patient is unable to tolerate a myeloablative conditioning regimen.

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Transplant, Policy No. 45.30
4. Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35
5. Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia, Transplant, Policy No. 45.40

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II gene loci on chromosome

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6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow (myeloablative chemotherapy). This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy (i.e., therapy that is intended to eliminate residual cancer cells after initial therapy) when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of *allogeneic* HCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and the subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. While such treatment may eliminate the malignant cells, patients are as likely to die from opportunistic infections, graft-versus-host disease (GVHD), and/or organ failure as from the underlying malignancy.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce adverse effects secondary to bone marrow toxicity, while retaining the beneficial graft-versus-malignancy effect of allogeneic transplantation. These regimens do not initially eradicate the patient's hematopoietic ability, allowing relatively prompt hematopoietic recovery (e.g., 28 days or less) even without a transplant. Patients who undergo RIC with allogeneic cell transplant initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC allotransplantation. They represent a continuum in their effects, from nearly totally myeloablation, to minimal myeloablation with lymphoablation.

Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality (NRM) and relapse due to residual disease. For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

TANDEM HCT

Tandem transplants usually are defined as the planned administration of two successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous

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hematopoietic stem cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use non-myeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.

NON-HODGKIN'S LYMPHOMA (NHL)

A heterogeneous group of lymphoproliferative malignancies, NHL usually originates in lymphoid tissue. Historically, uniform treatment of patients with NHL was hampered by the lack of a uniform classification system. In 1982, the Working Formulation (WF) was developed to unify different classification systems into one.[1] The WF divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type. Since our understanding of NHL has improved, the diagnosis has become more sophisticated and includes the incorporation of new immunophenotyping and genetic techniques. As a result, the WF has become outdated.

European and American pathologists proposed a new classification, the Revised European American Lymphoma (REAL) Classification[2], and an updated version of the REAL system, the new World Health Organization (WHO) classification.[3] The WHO classification recognizes three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and lymphoma.

Within the B-cell and T-cell categories, two subdivisions are recognized: precursor neoplasms, which correspond to the earliest stages of differentiation, and more mature differentiated neoplasms.

WHO CLASSIFICATION

The most recent lymphoma classification is the 2016 World Health Organization classification.[4]

Table 1. Updated WHO Classification (2016)

Classification of Neoplasms
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis[a]
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
· *Splenic diffuse red pulp small B-cell lymphoma*
· *Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma
· Waldenström macroglobulinemia
Monoclonal gammogapthy of undetermined significance, IgM[a]
Heavy chain diseases
· Alpha heavy chain disease
· Gamma heavy chain disease
· Mu heavy chain disease
Monoclonal gammogapthy of undetermined significance, IgG/IgA[a]
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunglobulin deposition diseases[a]

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Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma (MZL)
· *Pediatric nodal MZL*
Follicular lymphoma
· *In situ follicular neoplasia*[a]
· *Duodenal-type follicular lymphoma*[a]
Pediatric type follicular lymphoma[a]
· *Large B-cell lymphoma with IRF4 rearrangement*[a]
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
· *In situ mantel cell neoplasia*[a]
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
· *Germinal center B-cell type*[a]
· *Activated B-cell type*[a]
T-cell/histiocyte-rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK [anaplastic lymphoma kinase]-positive large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8 DLBCL NOS[a]
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration[a]
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements[a]
High-grade B-cell lymphoma, NOS[a]
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood[a]
Hydroa vacciniforme-like lymphoproliferative disorder[a]
Adult T-cell leukemia/ lymphoma
Extranodal NK/T-cell lymphoma, nasal type
EnteropathyassociatedT-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma[a]
Indolent T-cell lymphoproliferative disorder of the GI tract[a]
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder
· Lymphomatoid papulosis
· Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma[a]
Primary cutaneous acral CD8+ T-cell lymphoma[a]

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Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder[a]
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma[a]
Nodal peripheral T-cell lymphoma with TFH phenotype[a]
Anaplastic large-cell lymphoma (ALCL), ALK-positive
Anaplastic large-cell lymphoma (ALCL), ALK-negative[a]
Breast implant-associated anaplastic large-cell lymphoma[a]

[a] *Changes from 2008 WHO classification. Provisional entities are listed in italics.*

According to data from the National Cancer Data Base, the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 32.5%, follicular lymphoma (FL) 17.1%, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) 18.6%, mantle cell lymphoma (MCL) 4.1%, peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS) 1.7%, and marginal zone (MZL) lymphomas 5%. All other subtypes each represent less than 2% of cases of NHL.[5,6]

Several subtypes of NHL have emerged with the REAL/WHO classification with unique clinical and biologic features, and they will be addressed separately throughout the policy, when necessary (specifically MCL and PTCL).

In general, the NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages.[1] Early-stage indolent NHL (stage one or 2) may be effectively treated with radiation alone.[1] Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages.[1] These patients can often be re-treated if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma[7], and median survival with conventional chemotherapy is one year or less. Follicular lymphoma (FL) is the most common indolent NHL (70%–80% of cases), and often the terms indolent lymphoma and FL are used synonymously. Also included in the indolent NHL are SLL/CLL, lymphoplasmacytic lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.

Aggressive NHL has a shorter natural history; however, 30%–60% of these patients can be cured with intensive combination chemotherapy regimens.[1] Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt lymphoma.

Oncologists developed a clinical tool to aid in predicting the prognosis of patients with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI).[8] Prior to the development of IPI in 1993, prognosis was predominantly based on disease stage.

Based on the number of risk factors present and adjusted for patient age, the IPI defines four risk groups: low, low intermediate, high intermediate, and high risk, based on five significant risk factors prognostic of overall survival (OS):

- Age older than 60 years
- Elevated serum lactate dehydrogenase (LDH) level
- Ann Arbor stage III or IV disease
- Eastern Cooperative Oncology Group (ECOG) performance status of 2, 3, or 4
- Involvement of more than one extranodal site

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Risk groups are stratified according to the number of adverse factors as follows: 0 or 1 is low risk, 2 is low intermediate, 3 is high intermediate, and 4 or 5 are high risk.

Patients with two or more risk factors have a less than 50% chance of relapse-free (RFS) survival and OS at five years. Age-adjusted (aaIPI) and stage-adjusted modifications of this IPI are used for younger patients with localized disease.

Adverse risk factors for age-adjusted IPI include stage III or IV disease, elevated LDH and ECOG performance status of 2 or greater, and can be calculated as follows: 0 is low risk, 1 is low intermediate, 2 is high intermediate, and 3 is high risk.

With the success of the IPI, a separate prognostic index was developed for FL, which has multiple independent risk factors for relapse after a first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index (FLIPI) contains five adverse prognostic factors:

- Age older than 60 years
- Ann Arbor stage III-IV
- Hemoglobin level less than 12.0 g/dL
- More than four lymph node areas involved
- Elevated serum lactate dehydrogenase (LDH) level

These five factors are used to stratify patients into three categories of risk: low (0-1 risk factor), intermediate (two risk factors), or poor (three or more risk factors).[9]

Mantle Cell Lymphoma (MCL)

MCL comprises approximately 6%–8% of NHL, and has been recognized within the past 15 years as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed in 1992 by Banks [10] The number of therapeutic trials are not as numerous for MCL as for other NHL as it was not widely recognized until the REAL classification. MCL shows a strong predilection for elderly men, and the majority of cases (70%) present with disseminated (stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2–4 years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs, often within 12–18 months.[11] MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

There had been no generally established prognostic index for patients with MCL. Application of the IPI or FLIPI system to patients with MCL showed serious limitations, which included no separation of some important risk groups.[12] In addition, some of the individual IPI and FLIPI risk factors, including number of extranodal sites and number of involved nodal areas showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in patients with MCL.[12] Therefore, a new prognostic index for patients with MCL was developed, and should prove useful in comparing clinical trial results for MCL.

MCL international prognostic index (MIPI):

- Age
- ECOG performance status
- Serum LDH (calculated as a ratio of LDH to a laboratory’s upper limit of normal)

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- White blood cell count (WBC)
    - Zero points each are assigned for age younger than 50 years, ECOG performance 0–1, LDH ratio less than 0.67, WBC less than 6,700
    - One point each for age 50–59 years, LDH ratio 0.67–0.99, WBC 6,700–9,999.
    - Two points each for age 60–69 years, ECOG 2–4, LDH ratio 1.00–1.49, WBC 10,000–14,999
    - Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more

MIPI allows separation of three groups with significantly different prognoses:[12]

- 0–3 points=low risk, 44% of patients, median OS not reached and a five-year OS rate of 60%
- 4–5 points=intermediate risk, 35% of patients, median OS 51 months
- 6–11 points=high risk, 21% of patients, median OS 29 months

Peripheral T-Cell Lymphoma (PTCL)

Immature T-cell lymphomas are generally treated on leukemia protocols, whereas mature (peripheral) T-cell lymphomas are usually treated with chemotherapy regimens similar to those used in DLBCL.

PTCLs are less responsive to standard chemotherapy than DLBCLs and therefore carry a worse prognosis than aggressive B-cell counterparts. The poor results with conventional chemotherapy have prompted exploration of the role of HDC/SCT as first-line consolidation therapy.

STAGING

The Ann Arbor staging classification is commonly used for the staging of lymphomas and is the scheme defined in the American Joint Committee on Cancer (AJCC) Manual for Staging Cancer. Originally developed for Hodgkin's disease, this staging scheme was later expanded to include non-Hodgkin's lymphoma.

Staging of Lymphoma: Ann Arbor Classification

- Stage I

  Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)

- Stage II

  Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).

- Stage III

  Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)

- Stage IV

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Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of non-Hodgkin's lymphomas (NHL) are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of NHL, comparative clinical trials that compare this therapy with standard medical treatment, such as standard chemotherapy regimens, are needed. Further, for treatment of any of these lymphomas, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

This policy was initially based on four TEC Assessments.[13-16] Since that time, the classification of NHL has undergone significant changes, and several new and unique subtypes have emerged (e.g., mantle cell lymphoma [MCL], peripheral T-cell lymphoma [PTCL]).

INDOLENT LYMPHOMAS

HCT as First-Line Treatment for Indolent NHL

A number of systematic reviews and randomized trials have mostly failed to show improved outcomes with HCT as first-line treatment for indolent NHL. These are discussed below.

In 2012, Al Khabori performed a systematic review and meta-analysis of the use of autologous HCT in untreated, advanced follicular lymphoma.[17] Four randomized controlled trials (RCTs) comparing autologous HCT to conventional chemotherapy in 941 patients was included. Three trials reported overall survival (OS); moderate quality evidence from these trials did not show an improved OS with the use of HCT as part of the initial treatment of FL. Adverse outcomes including treatment-related mortality and the development of myelodysplastic syndrome, acute myeloid leukemia, and solid tumors, were not different between the two arms.

Schaaf conducted a systematic review and meta-analysis on the use of HCT for as treatment of follicular lymphoma (FL) for the Cochrane databases, published in 2012.[18] The researchers identified four trials focusing on HCT as first-line treatment for FL, the results of which are discussed individually below.[19-22] The primary outcome of the analysis was overall survival, and secondary outcomes included progression-free survival, treatment-related mortality, and secondary malignancies. After pooling results from the below trials, the authors concluded that there is no evidence to support the use of HCT for improved overall survival in first-line treatment of FL. Although improvements in treatment-related mortality and secondary malignancies were similarly not significantly associated with use of HCT, transplantation was significantly associated with improved progression-free survival in FL.

In a 2013 meta-analysis, Wang aimed to define the treatment effect of intensified therapy followed by autologous HCT compared with conventional therapy as first-line treatment of

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patients with FL in terms of OS and event-free survival (EFS).[23] The authors identified four randomized controlled trials that included 941 subjects. Results of the study indicated that no additional survival benefit was derived from the intensified therapy followed by autologous HCT. Authors did identify a significant benefit of intensified therapy followed by autologous HCT as first-line treatment in terms of EFS. Authors concluded that intensified therapy followed by autologous HCT does not improve the OS compared with conventional therapy.

In 2008, Ladetto reported the results of a Phase III, randomized, multicenter trial of patients with high-risk follicular lymphoma, treated at diagnosis.[19] A total of 134 patients were enrolled to receive either rituximab-supplemented high-dose chemotherapy (HDC) and autologous HCT or six courses of cyclophosphamide, doxorubicin (or Adriamycin®), vincristine (Oncovin®), and prednisolone (CHOP) followed by rituximab (CHOP-R). Of these patients 79% completed R-HDC and 71% completed CHOP-R. Complete remission was 85% with HCT and 62% with CHOP-R. At a median follow-up of 51 months, the four-year event-free survival (EFS) was 61% and 28% (HCT vs. CHOP-R, respectively), with no difference in overall survival (OS). Molecular remission (defined as negative results by polymerase chain reaction on two or more consecutive bone marrow samples spaced six months apart in patients who reached complete remission [CR]) was achieved in 80% of HCT and 44% of CHOP-R patients, and was the strongest independent outcome predictor. In 71% of the CHOP-R patients who had a relapse, salvage HCT was performed and achieved an 85% CR rate and a 68% three-year EFS. The authors concluded that there was no OS advantage to treating high-risk FL initially with HCT, but that relapsed/refractory FL would be the most appropriate setting for this therapy.

In 2006, Sebban reported the results of a randomized, multicenter study.[20] A total of 209 patients received cyclophosphamide, Adriamycin, etoposide, prednisolone (CHVP) plus interferon (CHVP-I arm) and 131 patients received CHOP followed by high-dose chemotherapy (HDC) with total body irradiation and autologous HCT. Response rates were similar in both groups (79% and 78% after induction therapy, respectively). After a median follow-up of 7.5 years, intent-to-treat analysis showed no difference between the two arms for OS (p=0.53) or EFS (p=0.11). The authors concluded that there was no statistically significant benefit to first-line, high-dose therapy in patients with follicular lymphoma, and that high-dose therapy should be reserved for relapsing patients.

Deconinck (2005) investigated the role of autologous HCT as initial therapy in 172 patients with follicular lymphoma considered at high risk due to the presence of either B symptoms (i.e., weight loss, fever, or night sweats), a single lymph node larger than 7 cm, more than three involved nodal sites, massive splenomegaly, or a variety of other indicators of high tumor burden.[21] The patients were randomized to receive either an immunochemotherapy regimen or a high-dose therapy followed by purged autologous HCT. While the autologous HCT group had a higher response rate and longer median EFS, there was no significant improvement in OS rate due to an excess of secondary malignancies. The authors concluded that autologous HCT cannot be recommended as the standard first-line treatment of follicular lymphoma with a high tumor burden.

In 2004, Lenz reported on the results of a trial of 307 patients with advanced stage lymphoma in first remission, including follicular lymphoma, mantle cell lymphoma, or lymphoplasmacytoid lymphoma.[22] Patients were randomized to receive either consolidative therapy with autologous HCT or interferon therapy. The five-year PFS rate was considerably higher in the autologous HCT arm (64.7%) compared to the interferon arm (33.3%). However, the median follow-up of patients is still too short to allow any comparison of OS.

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HCT for Relapsed, Indolent NHL

In the majority of patients with follicular lymphoma relapse, and with relapsed disease, cure is very unlikely, with a median survival of 4.5 years after recurrence.[24] A 2017 single-center retrospective study by Bozkaya analyzed data from 38 patients who were treated between 2004 and 2014 with high-dose chemotherapy followed by autologous stem cell transplantation.[25] All cases presented refractory or relapsed Hodgkin lymphoma (n=22) or a number of subtypes of non-Hodgkin lymphoma (n=18). Among the regimens given to patients were ifosfamide, carboplatin, and etoposide (ICE), and carmustine, etoposide, cytosine arabinoside, and melphalan (BEAM); additionally, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) were administered to Hodgkin lymphoma patients, and R-CHOP was given to those with non-Hodgkin lymphoma. Given the small sample size, multivariate analysis was precluded; however, univariate analysis found no statistically significant difference between groups, except in terms of chemosensitive vs chemoresistant cases and between patients undergoing ICE and BEAM regimens. After salvage therapy, 22 patients showed a partial response; six patients showed a complete response; and eight had stable disease. The study found that the five-year OS rate was significantly higher for chemosensitive patients (50%) than for chemoresistant patients (22%; p=0.02); however, given the small size of the population, other analyses were primarily descriptive in nature, or showed no statistical significance.

In the European CUP trial, 89 patients with relapsed, nontransformed follicular lymphoma with partial or complete response after standard induction chemotherapy were randomized to one of three arms: three additional cycles of conventional chemotherapy (n=24), HDC and unpurged autologous HCT (n=33), or HDC with purged autologous HCT (n=32). OS at four years for the chemotherapy versus unpurged versus purged arms was 46%, 71%, and 77%, respectively. Two-year PFS was 26%, 58%, and 55%, respectively. No difference was found between the two autologous HCT arms. Although several studies have consistently shown improved DFS with autologous HCT for relapsed follicular lymphoma, this study was the first to show a difference in OS benefit.[7]

Randomized trials have shown no survival advantage to HCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit of autologous HCT for relapsed disease.

AGGRESSIVE LYMPHOMAS

HCT for First-Line Therapy for Aggressive NHL

In 2018, Fossard published a retrospective multicenter analysis of the benefit of up-front autologous HCT for peripheral T-cell lymphoma.[26] A total of 269 patients with peripheral T-cell lymphoma-not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with partial or complete response after induction were included in the analysis. Of these, 134 patients were included in the autologous HCT intention-to-treat group and 135 were not. No statistically significant survival advantage in favor of HCT was identified and no outcome difference was identified between the groups for PFS or OS. A propensity score matching analysis taking into account age, LDH, PS, stage, B symptoms, histology, induction regimen, and response quality did not identify any significant differences. Further, subgroup analyses did not identify any other differences in response status, disease stage, or risk category.

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A 2017 single-center cohort study by Strüßmann compared high-dose chemotherapy with subsequent autologous HCT with an early intensified regimen (six-cycle CHOP-14) that included rituximab and methotrexate in 63 patients with diffuse large B-cell lymphoma and poor prognosis.[27] All patients had an age-adjusted IPI score of 2 or 3, and demographic information was comparable for both cohorts (median ages were 48 and 53 for cohorts 1 and 2, respectively). Four cycles of R-CHOP-21 were administered to cohort 1, followed by high-dose BEAM and autologous HCT; cohort 2 was initially given six-cycle CHOP-14, then rituximab and high-dose methotrexate. At two-year follow-up, PFS and OS rates were compared between cohorts, and patients in cohort 2 had significantly better outcomes, even when adjusted for multiple variables (including that of age-adjusted IPI score). Two-year PFS was 60.6% for those in cohort 1, compared with 93.37% in cohort 2 (hazard ratio [HR], 7.2; 95% CI, 1.64 to 31.75; p=0.009), a finding that retained statistical significance during multivariate analysis (HR=8.12; 95% CI, 1.73 to 36; p=0.006). The OS rate at two years was 69.7% for cohort 1 and 93.3% (HR=5.86; 95% CI. 1.28 to 26.8) after multivariate analysis. Also, patients in cohort 2 showed significantly higher overall response and complete remission rates (93.3% and 90%, respectively) than did patients in cohort 1 (66.7% and 63.6%); furthermore, no treatment-related mortality was reported for cohort 2 during follow-up, despite the initially intensive treatment protocol.

A 2017 phase 2 clinical trial (LNH2007-3B) by Casasnovas randomized 211 patients to receive a four-cycle regimen of either R-ACVBP or R-CHOP14, to be followed by either standard immunochemotherapy or autologous stem cell transplantation.[28] Of the 200 patients who completed the trial, 109 were assigned to R-ACVBP, and 97 were assigned to R-CHOP14; all patients had confirmed diffuse large B-cell lymphoma and had two or three risk factors according to age-adjusted IPI. Neither group achieved the primary endpoint, which was complete response (CR) greater than 50%, as defined by 2007 International Harmonization Project (IHP) criteria, with 47% (95% CI, 38% to 67%) of R-ACVBP patients and 39% (95% CI, 28% to 54%) showing CR. Investigators noted the disparity between the low response according to IHP criteria, and the improvement of outcomes predicted by positron emission tomography (PET) results and assessed by change in maximum standard uptake value (ΔSUVmax), suggesting that the latter may be a superior indicator of progression of disease than IHP criteria. PET scans were performed on all patients at baseline, after two cycles of the induction regimen (PET2), and again after four cycles of treatment (PET4); patients who showed negative results for both PET2 and PET4 were assigned to standard immunochemotherapy (n=51), while those who showed positive results for PET2 but negative results for PET4 were recommended for autologous HCT (n=40). No statistically significant differences in outcome were observed between these groups; however, investigators observed significant differences in outcomes when they assessed ΔSUVmax in patients. At measurement of PET2, rates of four-year PFS and OS were higher for patients with ΔSUVmax greater than 66% than for those showing a smaller change in SUVmax (PFS for the respective groups was 80% vs 56%, p<0.001; OS was 87% vs 69% in patients with ΔSUVmax <66%, p=0.003). When ΔSUVmax was assessed following PET4, similar improvements were observed: the four-year PFS rate was 84% in those showing ΔSUVmax greater than 70%, compared with 35% in those with ΔSUVmax of 70% of less (p<0.001); likewise, OS rates were 91% and 57% for the respective groups (p<0.001). Differences between the potential treatments (standard chemotherapy, autologous HCT, or salvage therapy) were insignificant.

Qualls published a small retrospective study in 2017 of 20 individuals (13 men, 7 women) who were treated with autologous stem cell transplantation for systemic non-Hodgkin lymphoma with some form of central nervous system (CNS) involvement.[29] Most patients presented with

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diffuse large B-cell lymphoma histology (n=17 [85%]), and CNS involvement varied: the two most common types of CNS involvement were parenchymal involvement (n=12 [60%]) and leptomeningeal disease (n=9 [45%]). As an induction regimen, the majority of patients (n=13 [65%]) were given R-CHOP, or, as treatment for CNS involvement, high-dose methotrexate (HD-MTX) (n=16 [80%]). The high-dose chemotherapy regimen for all patients included thiotepa, busulfan, and cyclophosphamide (TBC), and six patients received rituximab in addition to TBC; all patients received autologous stem cell transplantation during first complete remission. PFS rates were high at one-year (84%; 95% CI, 59% to 95%) and four-year (77%; 95% CI, 48% to 91%) follow-ups. OS rates were similarly high at one year 95%; 95% CI, 68% to 99%) and four years (82%; 95% CI, 54% to 94%). The most commonly experienced side-effect of the treatment was febrile neutropenia, which was observed in 80% (n=16) of patients. Despite the small size of the study, the authors noted the rare occurrence of relevant cases, suggesting that the high survival rates observed in the study supports the use of ASCT in the first complete remission.

Several randomized trials reported on between 1997 and 2002 compared outcomes of autologous HCT used to consolidate a first CR in patients with intermediate or aggressive non-Hodgkin's lymphoma (NHL), with outcomes of an alternative strategy that delayed transplants until relapse.[30-33] As summarized in an editorial, the preponderance of evidence showed that consolidating first CRs with HCT did not improve OS for the full population of enrolled patients.[34] However, a subgroup analysis at eight years' median follow-up focused on 236 patients at high or high-intermediate risk of relapse (based on age-adjusted International Prognostic Index [IPI] scores) who were enrolled in the largest of these trials (the LNH87-2 protocol; reference 19). The subgroup analysis reported superior overall (64% vs. 49%, respectively; relative risk 1.51, p=0.04) and DFS (55% vs. 39%, respectively; relative risk 1.56, p=0.02) for patients at elevated risk of relapse who were consolidated with an autologous HCT.[35]

A large, multigroup, prospective, randomized Phase III comparison of these strategies (the S9704 trial) is ongoing to confirm results of the subgroup analysis in a larger population with diffuse large B-cell lymphoma at high- and high-intermediate risk of relapse. Nevertheless, many clinicians view the LNH87-2 subgroup analysis[36] as sufficient evidence to support use of autologous HCT to consolidate a first CR when risk of relapse is high. In contrast, editorials[34,36] and recent reviews[37-39] agree that available evidence shows no survival benefit from autologous HCT to consolidate first CR in patients with intermediate or aggressive NHL at low- or low-intermediate risk of relapse (using age-adjusted IPI score).

Between 2005 and 2008, several reports of randomized trials showed no survival benefit to HCT as first-line therapy for aggressive lymphomas, as summarized below:

Greb (2008) undertook a systematic review and meta-analysis to determine whether HDC with autologous HCT as first-line treatment in patients with aggressive NHL improves survival compared to patients treated with conventional chemotherapy.[40] Fifteen randomized controlled trials (RCTs) including 3,079 patients were eligible for the meta-analysis. Thirteen studies with 2,018 patients showed significantly higher CR rates in the autologous HCT group (p=0.004). However, autologous HCT did not have an effect on OS when compared with conventional chemotherapy. According to the IPI, subgroup analysis of prognostic groups showed no survival differences between autologous HCT and conventional chemotherapy in 12 trials, and EFS also was not significantly different between the two groups. The authors

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concluded that despite higher CR rates, there is no benefit for autologous HCT as first-line treatment in aggressive NHL.

Betticher (2006) reported the results of a Phase III multicenter, randomized trial comparing sequential HDC with autologous HCT with standard CHOP as first-line therapy in 129 patients with aggressive NHL.[41] Remission rates were similar in the two groups, and after a median observation time of 48 months, there was no difference in OS with 46% in the sequential autologous HCT group and 53% in the group that received CHOP (p=0.48). The authors concluded that sequential autologous HCT did not confer any survival benefit as initial therapy in patients with aggressive NHL.

Baldissera (2006) reported on the results of a prospective RCT comparing HDC and autologous HCT to conventional chemotherapy as frontline therapy in 56 patients with high-risk aggressive NHL.[42] The five-year actuarial OS and PFS were not statistically different between the two study groups; only DFS was statistically different (97% vs. 47%, for the autologous HCT and conventional groups, respectively; p=0.02.)

Olivieri (2005) reported on a randomized study of 223 patients with aggressive NHL using upfront HDC with autologous HCT versus conventional chemotherapy (plus autologous HCT in cases of failure).[43] In the conventional group, 29 patients achieved a partial response or no response, and went on to receive HDC and autologous HCT. With a median follow-up of 62 months, there was no difference in seven-year probability of survival (60% and 57.8%; p=0.5), DFS (62% and 71%; p=0.2), and PFS (44.9% and 40.9%; p=0.7, respectively) between the two groups. The authors concluded that patients with aggressive NHL do not benefit from upfront autologous HCT.

In 2013, results of a Phase III multicenter randomized trial (SWOG-9704) of autologous HCT as consolidation for aggressive (high-intermediate or high-risk) diffuse B-cell NHL were published.[44] In this trial, 253 patients received five cycles of induction chemotherapy (CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone with [n=156, 47%] or without rituximab). Those who had at least a partial response to five cycles of induction therapy were randomly assigned to receive three additional cycles of CHOP (n=128) or one additional cycle of CHOP followed by autologous HCT (n=125). The primary efficacy end points of the trial were two-year PFS and OS. Two-year PFS rates were 69% and 55% in the HCT and control group, respectively (HR control vs HCT=1.72, 95% CI, 1.18 to 2.51, p=0.005). The two-year OS rates in the HCT and control group were 74% and 71%, respectively (HR=1.26, 95% CI, 0.82 to 1.94, p=0.30). Unplanned exploratory analyses showed a differential treatment effect according to disease risk level. Among high-risk patients, the two-year OS rate was 82% in the HCT group and 64% in the control group (log-rank test p=0.01). The main results of this trial compared with earlier study results in not discerning a significant effect of early autologous HCT on OS among a group of patients with high-intermediate- and high-risk diffuse B-cell NHL. However, it appears that the survival curve shows a plateau among the high-risk HCT patients out to perhaps 10 years after study registration. Although this evidence was from exploratory subset analysis, it further supports the medical necessity of this approach in such cases compared with nontransplant strategies.

HCT for Relapsed, Aggressive NHL

Autologous HCT is the treatment of choice for relapsed or refractory aggressive NHL for patients who achieve a complete or partial response with second-line therapy.[1,5,6]

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Data from randomized trials have shown conflicting results, but some have shown an overall survival benefit with HCT to consolidate a first CR in patients with aggressive B-cell lymphomas at high or high-intermediate risk of relapse.

HCT for relapsed aggressive B-cell lymphomas is the treatment of choice, as randomized studies have shown an overall survival benefit with this approach.

TANDEM TRANSPLANTS

Nonrandomized Studies

Monjanel reported on a pilot Phase II trial evaluating tandem high-dose therapy with stem-cell support between 1994 and 1999 in 45 patients with age adjusted-IPI equal to three untreated aggressive non-Hodgkin's lymphoma.[45] After induction, responders underwent tandem autologous transplantation; 31 out of 41 evaluable patients completed the program. There were four toxic deaths. The primary end point of the study was complete response rate, which was 49%. With a median follow-up of 114 months for surviving patients, the OS was 51%, and 19 of the 22 patients (86%) who reached a complete response were alive and relapse-free. Prospective evaluation of quality of life and comorbidities of surviving patients did not reveal long-term toxicities. The authors concluded that in the era of monoclonal antibodies and response-adapted therapy, the role of tandem transplantation still needs to be determined.

In a 2005 pilot study reported by Papadopoulos, 41 patients with poor-risk NHL and Hodgkin's disease were given tandem HDC with autologous HCT.[46] Thirty-one patients (76%) completed both transplants. Overall toxic death rate was 12%. The study evaluated the maximum tolerated dose of the chemotherapeutic regimen, and did not compare tandem versus single transplants for NHL.

Tarella (2007) reported on a multicenter, non-randomized, prospective trial consisting of 112 patients with previously untreated diffuse large B-cell lymphoma and age-adjusted IPI score of 2-3.[47] All patients received rituximab-supplemented, early-intensified HDC with multiple autologous HCT. Although the study concluded the treatment regimen improved patients' life expectancy, the comparisons were made with historic controls that had received conventional chemotherapy.

A retrospective analysis by Crocchiolo (2013) of 34 high-risk NHL patients who underwent autologous HCT followed closely by reduced-intensity allogeneic HCT ("tandem auto-allo") included patients treated from 2002 to 2010.[48] In this study, researchers began to identify appropriate allogeneic donors at the initiation of the salvage regimen. The patients' median age was 47 years. Histologic subtypes were: diffuse large B-cell (n=5), follicular (n=14), transformed follicular (n=4), mantle-cell (n=5), plasmacytoid lymphoma (n=1), anaplastic large T-cell (n=2), and peripheral T-cell (n=3). HLA-identical sibling donors were located for 29 patients, and 10/10-matched unrelated individuals were identified for five cases. The median interval between autologous HCT and allogeneic HCT was 77 days (range 36–197 days). At a median follow-up of 46 months since allogeneic HCT, the five-year OS was 77% and PFS was 68%. Six patients experienced disease relapse or progression, the 100-day TRM was 0%, and two-year TRM incidence was 6%. These results suggest tandem autologous-allogeneic transplantation appears feasible in high-risk NHL patients having a HLA-identical donor, but further study is necessary to establish its role in this setting.

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No randomized studies have been conducted on the use of tandem HCT for the treatment of non-Hodgkin's lymphomas, and the published data consist of small numbers of patients. Therefore, the data on tandem transplants is insufficient to determine outcomes with this type of treatment.

ALLOTRANSPLANT AFTER A FAILED AUTOTRANSPLANT

An updated literature search found no prospective randomized controlled studies comparing allotransplants to alternative strategies for managing failure (progression or relapse) after an autologous HCT for NHL. The scant data are insufficient to change conclusions of the previous TEC Assessment.[15]

The paucity of outcomes data for allotransplants after a failed autologous HCT is not surprising. Patients are rarely considered eligible for this option either because their relapsed lymphoma progresses too rapidly, because their advanced physiologic age or poor health status increases the likelihood of adverse outcomes (e.g., from graft-versus-host-disease), or because they lack a well-matched donor. Nevertheless, several institutions report that a minority of patients achieved long-term DFS following an allotransplant for relapsed NHL after an autotransplant. Factors that apparently increase the likelihood of survival include a chemosensitive relapse, younger age, a long disease-free interval since the prior autotransplant, availability of an HLA-identical sibling donor, and fewer chemotherapy regimens prior to the failed autotransplant. Thus, clinical judgment can play an important role to select patients for this treatment with a reasonable likelihood that potential benefits may exceed harms.

NHL SUBTYPES NEWLY DEFINED BY THE WHO CLASSIFICATION

Mantle Cell Lymphoma (MCL)

In an attempt to improve the outcome of MCL, several Phase II trials investigated the efficacy of autologous HCT, with published results differing substantially.[12,49] Some studies found no benefit to HCT, suggested an EFS advantage, at least in a subset of patients.[12] The differing results in these studies were likely due to different time points of transplant (first vs. second remission) and other patient selection criteria.[49]

In 2005, the results of the first randomized trial were reported by Dreyling of the European MCL Network.[49] A total of 122 patients with MCL received either autologous HCT or interferon as consolidation therapy in first CR or PR. Among these patients, 43% had a low-risk, 11% had a high-intermediate risk, and 6% had a high-risk profile. Autologous HCT resulted in a PR rate of 17% and a CR rate of 81% (versus PR of 62% and CR of 37% with interferon). Survival curves for time to treatment failure (TTF) after randomization showed that autologous HCT was superior to interferon (p=0.0023). There also was significant improvement in the three-year PFS demonstrated in the autologous HCT versus interferon arm (54% and 25%, respectively; p=0.01). At the time of the reporting, no advantage was seen in OS, with a three-year OS of 83% versus 77%. The trial also suggested that the impact of autologous HCT could depend on the patient's remission status prior to the transplant, with a median PFS of 46 months in patients in CR versus 33 months in patients in PR.

García-Noblejas (2017) conducted a retrospective analysis of MCL patients who received autologous stem cell transplantation.[50] They found, at a mean follow-up of 54 months, progression-free survival and overall survival to be 38 and 74 months, respectively. They

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stratified patients as achieving CR before the transplant or not. For patients who were in CR at the time of the transplant, progression-free survival and overall survival were 49 and 97 months, respectively.

Jantunen (2011) investigated the feasibility and efficacy of autologous HCT in patients with MCL older than 65 years. In the retrospective comparison, there were no differences in relapse rate, PFS, or OS between patients with MCL under 65 years of age and the seventy-nine patients ≥65 years of age.[51]

In an International Bone Marrow Transplant Registry (IBMTR) study, 212 patients (median age 50 years) received allogeneic transplants.[52] At two years, OS was only 40%. In a study by the European Bone Marrow Transplant Group, 22 allogeneic transplant patients had EFS and OS rates of 50% and 62%, respectively, but the follow-up was too short.[53]

The literature regarding allogeneic transplantation in mantle cell lymphoma is limited. This is due, in part, to the fact that the average age of patients at diagnosis is 65 years, making them unsuitable for allogeneic transplant. In addition, the disease is relatively rare, and hence, randomized studies on the use of HCT have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with the use of autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Although a graft-versus-tumor effect has been demonstrated[54], there is currently no conclusive evidence that allogeneic transplantation is curative in mantle cell lymphoma.[55]

There have been several studies regarding reduced-intensity chemotherapy (RIC) and allogeneic HCT.[55]

Khouri reported on results of RIC allogeneic HCT in 18 patients with mantle cell lymphoma, and after a median follow-up of 26 months, the actuarial probability of EFS was 82% at three years.[56] Maris evaluated allogeneic HCT in 33 patients with relapsed and recurrent mantle cell lymphoma. At two years, the relapse and nonrelapse mortality rates were 9% and 24%, respectively, and the OS and DFS were 65% and 60%, respectively.[57] Cook retrospectively evaluated outcomes of RIC allogeneic HCT in 70 MCL patients. The five-year overall survival (OS) and progression-free survival (PFS) rates were 37% and 14% respectively. The one- and five-year non-relapse mortality (NRM) was 18% and 21% respectively.[58]

Till (2008) reported the results of the outcomes of 56 patients with MCL, treated with high-dose induction chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD) with or without rituximab followed by autologous HCT in first CR or PR (n=21), cyclophosphamide, doxorubicin (or Adriamycin), vincristine (Oncovin), and prednisolone (CHOP) with or without rituximab followed by autologous HCT in first CR or PR (n=15), or autologous HCT following disease progression (n=20).[59] OS and PFS at three years among patients transplanted in CR or PR were 93% and 63% compared with 46% and 36%, all respectively, for patients transplanted with relapsed/refractory disease. The hazard of mortality among patients transplanted with relapsed or refractory disease was 6.1 times that of patients transplanted in first CR or PR (p=.0006).

Geisler (2008) reported on 160 previously untreated patients with MCL with dose-intensified induction immunochemotherapy.[60] Responders received HDC with in vivo purged autologous HCT. Overall and CR was achieved in 96% and 54%, respectively. The six-year OS, EFS, and PFS were 70%, 56%, and 66%, respectively, with no relapses occurring after five years.

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Evens reported on 25 untreated patients with MCL who received intensive induction chemotherapy, with an overall response rate of 74%.[61] Seventeen patients received a consolidative autologous (n=13) or allogeneic (n=4) HCT. Five-year EFS and OS for all patients was 35% and 50%, respectively. After a median follow-up of 66 months, the five-year EFS and OS for patients who received autologous HCT was 54% and 75%, respectively.

Budde (2011) evaluated outcomes of 118 consecutive patients with MCL who received a high-dose induction regimen before autologous HCT. The authors report that the intensive induction regimen was not associated with improved survival in the overall study population or any of the subgroups (i.e., patients who underwent autologous HCT as initial consolidation, or patients under 60 years of age).[62]

A 2007 review article by Kasamon summarized the literature on high-dose therapy for mantle cell lymphoma, and a repeat finding in several studies has been a superior result of transplantation in first CR (autologous or allogeneic) rather than in the relapsed setting.[12]

Due in part to the relative rarity of the disease, randomized studies on the use of HCT in MCL have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with the use of autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allogeneic HCT has shown prolonged disease control in the relapsed/refractory setting.

Peripheral T-Cell Lymphoma (Mature T-cell or NK-cell neoplasms)

Prospective studies with autologous HCT in patients with aggressive PTCL consist of only a few studies with small numbers of patients. A few retrospective studies have included a moderate number of patients and length of follow-up.

Wang (2018) conducted a retrospective study to investigate the efficacy of autologous HCT as first-line therapy for treating extranodal natural killer/T-cell lymphoma.[63] All patients in the study were newly diagnosed with ENKTL. The high-dose chemotherapy plus autologous HCT (study) group included 20 patients and the control group included 60 ENKTL patients who were not willing to receive high-dose chemotherapy and autologous HCT. All patients were under the age of 60, high risk, and fit for high-dose chemotherapy and autologous HCT. All patients received induction chemotherapy with or without involved-field radiotherapy. The median follow-up time was 61.0 months. The difference between groups in OS was statistically significant (p=0.026) at five years post-diagnosis, but not at three or two years (p=0.233 and p=0.054, respectively). While the median OS of the study group was not reached, the median OS of the control group was 62.0 months. In the study group, no treatment-related mortality occurred.

Rohlfing (2018) performed a single-center retrospective analysis of first-line HCT in patients diagnosed with PTCL.[64] Patients diagnosed with T-cell leukemias, ALCL ALK+, and primary cutaneous lymphomas except ALCL ALK- were excluded. Of the 97 patients included in the final analysis, autologous HCT in the first remission was intended for 63 patients (intention-to-treat group; ITT) and 34 patients were not intended to be transplanted (no intention-to-treat group; nITT). Reasons for forgoing transplant included comorbidity, higher age, low International Prognostic Index (IPI), physician’s decision, and unknown reasons. Baseline differences between the groups included age and fraction of patients receiving induction other than CHOP/CHOEP (CHOP plus etoposide; both higher in nITT) and proportion of patients

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with elevated lactate dehydrogenase (smaller in nITT). Of those in the ITT group, 54% underwent transplantation. Five-year OS and PFS were not statistically different between groups (46 and 23% in the ITT and group and 42 and 25% in the nITT group, respectively). In a multivariate analysis that adjusted for gender, age, IPI, PTCL subtype, and ITT, the only factor associated with significant benefits for OS was younger age.

Yam (2017) retrospectively analyzed PTCL patients receiving either active observation (28 patients) or consolidation with autologous stem cell transplantation (20 patients). Three-year PFS was 37% and 41% for observation and transplant groups, respectively. The one-year cumulative incidence of relapse and the median PFS was not significantly different between the groups, with one-year cumulative incidence of relapse in the observation and transplant groups at 50% and 46%, respectively and median progression-free survival in the observation and ASCT groups at 15.8 and 12.8 months, respectively.

Han (2017) analyzed clinical data from 46 patients with PTCL receiving autologous stem cell transplantation as consolidation therapy.[65] Thirty-four patients with pre-transplantation CR and 12 with PR received transplantation. Median follow-up was 37 months. The five-year OS and PFS rates were 77.1% and 61.9%, respectively.

A prospective Phase II trial by Rodriguez (2007) showed that autologous HCT as first-line consolidation therapy improved treatment outcome in patients responding to induction therapy.[66] Nineteen of 26 patients who showed CR or partial response to induction therapy received an autotransplant. At two years post-transplant, OS, PFS, and DFS were 84%, 56%, and 63%, respectively.

The role of HCT in peripheral T-cell lymphoma is not well defined. Few studies have been conducted, mostly retrospectively and with small numbers of patients.[67-81] This is partly due to the rarity and heterogeneity of this group of lymphomas. In particular, studies often mix patients with PTCL-NOS (which has a poorer prognosis) with patients with ALK + ALCL which has a better prognosis (even with conventional chemotherapy regimens), and ALK- ALCL patients who have a worse prognosis than ALK+ ALCL but better than PTCL-NOS patients. There have been no randomized studies comparing chemotherapy regimens solely in patients with PTCL (i.e., some randomized studies have included PTCL with aggressive B-cell lymphomas). For frontline therapy, results from recent phase II studies with autologous HCT as consolidation offers the best survival outcomes for patients with high-risk features; however, randomized trials to confirm these findings have not been performed. No relevant data for the use of allogeneic HCT in the front-line setting are available. Patients with relapsed or refractory PTCL are generally considered incurable with chemotherapy alone. In the salvage setting, the data show that the use of HCT may improve survival outcomes similar to the results observed in corresponding aggressive B-cell lymphomas in the same treatment setting.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

Guidelines from NCCN offer the following on the use of HCT in NHL:[5,6,82]

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Follicular Lymphoma (grade 1-2)

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For histologic transformation to diffuse large B-cell lymphoma with either multiple prior therapies or minimal or no prior chemotherapy, high-dose therapy with autologous stem cell rescue or allogeneic cell transplant may be considered. It is strongly recommended this treatment be given in the context of a clinical trial.

A second-line consolidation suggested treatment includes allogeneic cell transplant for highly selected patients.

Mantle Cell Lymphoma

In stage II bulky, III, and IV aggressive mantle cell lymphoma candidates for high-dose therapy with autologous stem cell rescue following a complete response, autologous cell rescue is recommended as first-line consolidative therapy; allogeneic cell transplant may be considered as for second-line consolidation.

Diffuse Large B-Cell Lymphoma

For stage I and II diffuse large B-cell lymphoma follow-up therapy for a partial response may include high-dose therapy with autologous stem cell rescue, or clinical trial which may include allogeneic cell transplant.

For relapsed/refractory disease in patients who are candidates for high-dose therapy, following second-line therapy, consolidation therapy may include high-dose therapy with autologous stem cell rescue or allogeneic hematopoietic cell transplant in select cases for those who have a complete or partial response.

Peripheral T-cell Lymphoma

Consider consolidation with high-dose therapy and stem cell rescue as first-line consolidation therapy in peripheral T-cell lymphoma patients showing a complete response to induction therapy (except those considered low-risk, e.g., ALCL ALK-positive). For relapse/refractory disease, in patients who intend to proceed to transplant and who have a complete or partial response to additional therapy, additional/consolidation therapy may include allogeneic cell transplant (non-myeloablative or ablative) or high-dose therapy with autologous stem cell rescue.

Mycosis Fungoides/Sezary Syndrome

For refractory or progressive disease in stage IIB, III, IV mycosis fungoides/Sezary syndrome patients, consider allogeneic HCT. “Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant.”

Adult T-cell Leukemia/Lymphoma

Following initial response, after two cycles, consider allogeneic cell transplant in adult T-cell leukemia/lymphoma patients.

SUMMARY

Research has shown improved survival (overall survival and/or progression-free survival) from hematopoietic cell transplantation (HCT) for non-Hodgkin’s lymphomas in cases other than initial treatment. Therefore, HCT (autologous or allogeneic), including reduced intensity

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conditioning allogeneic HCT when criteria are met, for these indications may be considered medically necessary.

Research has not shown improved survival from hematopoietic cell transplantation (HCT) as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for treatment of non-Hodgkin's lymphomas. Therefore, HCT (autologous or allogeneic) is considered investigational for this indication.

No randomized studies have been conducted on the use of tandem hematopoietic cell transplantation (HCT) for the treatment of non-Hodgkin's lymphomas. There is not enough research to know if this treatment is safe and effective. Therefore, tandem HCT is considered investigational to treat patients with any stage, grade, or subtype of non-Hodgkin's lymphomas.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.24

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Effective: December 1, 2019

Next Review: August 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic hematopoietic cell transplant (using either reduced-intensity conditioning [RIC], or myeloablative conditioning), may be considered **medically necessary** to treat either of the following (A. or B.):
   A. Myelodysplastic syndromes; or
   B. Myeloproliferative neoplasms.

II. Subsequent allogeneic hematopoietic cell transplant using myeloablative conditioning after a previous allogeneic hematopoietic cell transplant with reduced intensity conditioning is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

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DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

ALLOGENEIC HCT

Allogeneic HCT may be considered for patients as follows:

Table 1 summarizes the NCCN recommendations for allogeneic HCT to treat Myelodysplastic Syndromes [v.2.2019]):

Table 1: NCCN Guidelines for Allo-HCT for Myelodysplastic Syndromes

Prognostic Category	Recommendations for HCT
IPSS low/intermediate-1 OR IPSS-R very low, low, intermediate OR WPSS very low, low, intermediate OR	Consider allo-HCT for patients who have clinically relevant thrombocytopenia or neutropenia or increased marrow blasts, with disease progression or no response after azacitidine/decitabine or immunosuppressive therapy Consider allo-HCT for patients who have symptomatic anemia with no 5q deletion, with serum erythropoietin level >500 mU/mL, with poor probability of response to immunosuppressive therapy, and no response or intolerance to azacitidine/decitabine or immunosuppressive therapy
IPSS intermediate-2, high OR IPSS-R intermediate, high, very high OR WPSS high, very high	Recommend allo-HCT if a high-intensity therapy candidate and transplant candidate and donor stem cell source is available

allo: allogeneic; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; NCCN: National Comprehensive Cancer Network; WPSS: WHO Classification-based Prognostic Scoring System.

Table 2 summarizes the NCCN recommendations for the use of allogeneic HCT (allo-HCT) for the treatment of myeloproliferative neoplasms (MPN; v.2.2019).[1] The guideline notes that selection of allo-HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.

Table 2: NCCN Guidelines for Allo-HCT for Myeloproliferative Neoplasms

Prognostic Category	Recommendations for Allo-HCT
Intermediate risk – 1 myelofibrosis IPSS=1 DIPSS-Plus=1 DIPSS=1 or 2	Observation or Ruxolitinib if symptomatic or allo-HCT
Intermediate risk – 2 myelofibrosis IPSS=2 DIPSS-Plus=2 or 3	Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

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Prognostic Category	Recommendations for Allo-HCT
DIPSS=3 or 4 High-risk myelofibrosis IPSS≥3 DIPSS-Plus=4 to 6 DIPSS=5 or 6	
Disease progression to advanced stage/AML	Induce remission with hypomethylating agents or intensive induction chemotherapy followed by allo-HCT

allo: allogeneic; AML: acute myeloid leukemia; DIPSS: Dynamic International Prognostic Scoring System; HCT: hematopoietic cell transplantation; IPSS: International Prognostic Scoring System; NCCN: National Comprehensive Cancer Network.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, Transplant, Policy No. 45.28
4. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of

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chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) refer to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into acute myelocytic leukemia (AML). MDS can occur as a primary (idiopathic) disease, or be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40%–60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. The vast majority of MDS diagnoses occur in individuals over the age of 55–60 years, with an age-adjusted incidence of about 62% among individuals over age 70 years. Patients either succumb to disease progression to AML or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do

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other patients.

Risk Stratification of MDS

Risk stratification for MDS is performed using the IPSS (see Table PG1). This system was developed after pooling data from seven studies that used independent, risk-based prognostic factors. The prognostic model and the scoring system were built based on blast count, degree of cytopenia, and blast percentage. Risk scores were weighted relative to their statistical power. This system is widely used to divide patients into two categories: (1) low-risk and (2) high-risk groups (see Table PG2). The low-risk group includes low-risk and Int-1 IPSS groups; the goals in low-risk MDS patients are to improve quality of life and achieve transfusion independence. In the high-risk group—which includes intermediate-2 and high-risk IPSS groups—the goals are slowing the progression of disease to acute myeloid leukemia (AML) and improving survival. IPSS is usually calculated on diagnosis. The role of lactate dehydrogenase, marrow fibrosis, and β2-microglobulin also should be considered after establishing IPSS. If elevated, the prognostic category becomes worse by 1 category change.

Table PG1. International Prognostic Scoring System: Myelodysplastic Syndrome Prognostic Variables

Variable	0	0.5	1.0	1.5	2.0
Marrow blasts, %	<5%	5%-10%	–	11%-20%	21%-30%
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3	–	–	–

Table PG2. International Prognostic Scoring System: Myelodysplastic Syndrome Clinical Outcomes

Risk Group	Total Score	Median Survival, y	Time for 25% to Progress to AML, y
Low	0	5.7	9.4
Intermediate-1	0.5-1.0	3.5	3.3
Intermediate-2	1.5-2.0	1.2	1.12
High	≥2.5	0.4	0.2

AML: acute myelocytic leukemia.

Since 1997, the International Prognostic Scoring System (IPSS) has been used to assess prognosis of primary untreated adult MDS patients. The IPSS were refined in 2012 by Greenberg and is referred to as the IPSS-R. Five prognostic subgroups were specified, expanding on the IPSS four group classification. Patient age, performance status, serum ferritin, and lactate dehydrogenase were included in the development of this system for survival but not for acute myeloid leukemia transformation.[2] The cytogenetic classification of the IPSS-R has since been found to have added value in predicting patient outcomes as compared to prediction models using only the traditional risk factors or the three-group IPSS cytogenetic classification.[3]

The WHO subgroup classification adds morphologic refinement of the French-American-British (FAB) classification. The WHO Prognostic Scoring System (WPSS) accounts for blast percentage, cytogenetics, and severity of cytopenias as assessed by transfusion requirements.

MDS Treatment

Treatment of smoldering or nonprogressing MDS has in the past involved best supportive care including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. A diverse array of therapies are now available to treat MDS, including hematopoietic growth factors (e.g., erythropoietin, darbepoetin, granulocyte colony-stimulating factor), transcriptional-modifying

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therapy (e.g., U.S. Food and Drug Administration [FDA]-approved hypomethylating agents, non-approved histone deacetylase inhibitors), immunomodulators (e.g., lenalidomide, thalidomide, antithymocyte globulin, cyclosporine A), low-dose chemotherapy (e.g., cytarabine), and allogeneic HCT. Given the spectrum of treatments available, the goal of therapy must be decided upfront, whether it is to improve anemia, thrombocytopenia, or neutropenia; eliminate the need for RBC transfusion; achieve complete remission (CR); or, cure the disease. Allogeneic HCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's risk preference, and severity of MDS at presentation.

MYELOPROLIFERATIVE NEOPLASMS

The MPNs are clonal bone marrow stem-cell disorders characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. They share a common stem cell-derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of mutations that affect protein tyrosine kinases or related molecules. The unifying characteristic common to all MPNs is effective clonal myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

As a group, about 8,400 MPNs are diagnosed annually in the U.S. Like MDS, MPNs occur primarily in older individuals, with about 67% reported in patients aged 60 years and older. In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Myeloablative allogeneic HCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often severe treatment-related adverse effects of this procedure. However, the use RIC of conditioning regimens for allogeneic HCT has extended the potential benefits of this procedure to selected individuals with these disorders.

MPN Classification and Risk Stratification

In 2008, a new WHO classification scheme replaced the term chronic myeloproliferative disorder (CMPD or MPD) with the term myeloproliferative neoplasms (MPN). The 2016 classification update is not a significant change in disease categories, but rather, an incorporation of the new knowledge of the diseases accumulated since 2008.[4] The myeloproliferative neoplasms include:

- Chronic myeloid leukemia (CML)
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
- Essential thrombocytopenia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable
- Mastocytosis

See Appendix I for the full WHO myeloid neoplasm and acute leukemia classification.

Amongst each of the MPNs, risk stratification is based on clinical findings at diagnosis. For primary myelofibrosis, post-PV, or post-ET MF, the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), or DIPSS-PLUS may be

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used. Other factors such as age and history of thrombosis factor in to other MPN risk stratification.

MPN Treatment

In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera and intermediate- and high-risk primary myelofibrosis.

In November 2011, the FDA approved the orally-administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib has been associated with improved OS, spleen size, and symptoms of myelofibrosis when compared with placebo.[5]

NOTES:

- Chronic myeloid leukemia and acute myeloid leukemia are considered in separate medical policies (see Cross References).
- For additional information regarding MDS and MPN classification see the WHO strata listed in Appendix I.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HST for treatment of myelodysplastic syndromes and myeloproliferative neoplasms, clinical trials that compare HCT using either a myeloablative or reduced intensity conditioning regimen to standard medical treatments are needed. Further, for treatment of malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

MYELODYSPLASTIC SYNDROMES (MDS)

Despite the successes seen with new drugs now available to treat MDS (e.g., decitabine, azacitidine, lenalidomide), allogeneic HCT is the only treatment capable of complete and permanent eradication of the MDS clone.[6] The recommendations of a systematic review of the role of allogeneic HCT in patients with MDS prepared by the American Society for Blood and Marrow Transplantation (ASBMT) are congruent with the present policy statements.[7] Other reviews concur with the ASBMT recommendations.[8-10] For example, a review of allogeneic HCT using myeloablative conditioning for MDS included 24 studies (prospective and retrospective) published between 2000 and 2008 that included a total 1,378 cases with age range of 32–59 years.[11] A majority of patients (n = 885) received matched related donor (MRD) allogeneic HCT, with other donor types including syngeneic, matched, unrelated donor (MUD), mismatched unrelated donor (URD), and umbilical cord blood. Most studies included

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de novo and secondary MDS, chronic myelomonocytic leukemia, and myeloproliferative neoplasms (MPNs), de novo and secondary acute myelocytic leukemia (AML) and transformed AML. Peripheral blood and bone marrow stem-cell grafts were allowed in most studies. The most commonly used conditioning regimens were busulfan plus cyclophosphamide (BU/CY) and CY plus total body irradiation (CY/TBI), with cyclosporine A (CYA) used for graft-versus-host disease (GVHD) prophylaxis. Length of follow-up ranged from five months to about eight years. Grades II-IV acute GVHD varied from 18% to 100%. Relapse risk ranged from a low of 24% at one year to 36% at five years. Overall survival (OS) ranged from 25% at two years to 52% at four years, with non-relapse mortality (NRM) ranging from 19% at day 100 to 61% at five years.

Smaller studies continue to report outcomes from HCT for MDS in variety of patient populations and to evaluate the impact of specific patient, conditioning, and donor characteristics on outcomes.[12-20]

A growing body of evidence from more than 30 largely heterogeneous uncontrolled studies of reduced intensity conditioning (RIC) with allogeneic HCT shows long-term remissions (i.e., longer than four years) can be achieved, often with reduced treatment-related morbidity and mortality, in patients with MDS/AML who otherwise would not be candidates for myeloablative conditioning regimens.[11,21-36] These prospective and retrospective studies included cohorts of 16–215 patients similar to those in the myeloablative allogeneic HCT studies. The most common conditioning regimens used were fludarabine based, with CYA and tacrolimus used for GVHD prophylaxis. The reported incidence of grades II–IV GVHD was 9-63%, with relapse risk of 6–61%. The OS rates ranged between 44% at one year to 46% at five years, with a median follow-up range of 14 months to over four years.

In general, these RIC trials showed a low rate of engraftment failure and low NRM, but at the cost of a higher relapse rate than with myeloablative allogeneic HCT. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with myeloablative and RIC regimens with allogeneic HCT. Furthermore, no randomized trials have been published in which RIC with allogeneic HCT has been compared with conventional chemotherapy alone, which has been the standard of care in patients with MDS/AML for whom myeloablative chemotherapy and allogeneic HCT are contraindicated. Nonetheless, given the absence of curative therapies for these patients, RIC allogeneic HCT may be a treatment option for patients with MDS who could benefit from allogeneic HCT but who for medical reasons (see Policy Guidelines) would be unable to tolerate a myeloablative conditioning regimen.

MYELOPROLIFERATIVE NEOPLASMS (MPN)

Data on therapy for MPN remain sparse.[28,30,37] As outlined previously in this policy, with the exception of myeloablative chemotherapy and allogeneic HCT, no therapy has yet been proven to be curative or to prolong survival of patients with MPN. The significant toxicity of myeloablative conditioning and allogeneic HCT in MPN has led to study of the use of RIC regimens for these diseases.

Kroger compared outcomes for patients treated with allo-HCT (n=190) or conventional therapies (n=248) at diagnosis in patients with primary myelofibrosis who were under 65 years old at diagnosis.[38] In the HCT group, 91 and 97 subjects received RIC and MA conditioning, respectively. Patients at low risk based on the Dynamic International Prognostic Scoring System model treated with HCT had a relative risk of death, compared with conventionally

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treated patients, of 5.6 (95% CI, 1.7 to 19; p=0.005). In contrast, those with intermediate-2 and high risk treated with HCT had a relative risk of death, compared with conventionally treated patients, of 0.55 (95% CI, 0.36 to 0.83; p=0.005) and 0.37 (95% CI, 0.21 to 0.66; p<0.001), respectively. Intermediate-1 patients treated with HCT did not significantly differ in risk of death from those treated with conventional therapies. Although the study design was limited by the potential for bias due to patient selection, these results support using prognosis to guide decisions about HCT for primary myelofibrosis.

The largest study of allogeneic HCT for primary myelofibrosis comes from retrospective analysis of the outcomes of 289 patients treated between 1989 and 2002, from the database of the Center for International Bone Marrow Transplant Research (CIBMTR).[39] The median age was 47 years (range: 18-73 years). Donors were HLA-identical siblings in 162 patients, unrelated individuals in 101 patients, and HLA non-identical family members in 26 patients. Patients were treated with a variety of conditioning regimens and GVHD prophylaxis regimens. Splenectomy was performed in 65 patients prior to transplantation. The 100-day treatment-related mortality was 18% for HLA identical sibling transplants, 35% for unrelated transplants, and 19% for transplants from alternative related donors. Corresponding five-year OS rates were 37%, 30%, and 40%, respectively. DFS rates were 33%, 27%, and 22%, respectively. DFS for patients receiving reduced-intensity transplants was comparable: 39% for HLA identical sibling donors and 17% for unrelated donors at three years. In this large retrospective series, allogeneic transplantation for myelofibrosis resulted in long-term relapse-free survival (RFS) in about one-third of patients.

One case series of 148 patients included 27 (mean age: 59 years) with MPN who underwent allogeneic HCT using a RIC regimen of low-dose (2 Gy) total body irradiation alone or with the addition of fludarabine.[31] At a median follow-up of 47 months, the three-year relapse-free survival was 37% and overall survival was 43%, with a three-year nonrelapse mortality of 32%.

In a second series, 103 patients (median age 55 years, range 32-68 years) with intermediate to high risk (86% of total patients) primary myelofibrosis (PMF) or post-essential thrombocythemia (PT) and polycythemia vera myelofibrosis (PVM) were included on a prospective multicenter Phase II trial to determine efficacy of a busulfan plus fludarabine-based RIC regimen followed by allogeneic HCT from related (n=33) or unrelated (n=70) donors.[40] Acute grade II-IV GVHD occurred in 27%, and chronic GVHD in 43% of patients. The cumulative incidence of NRM at one year in all patients was 16% (95% confidence interval [CI], 9-23%) but reached 38% (95% CI, 15-61%) among those with a mismatched donor versus 12% (95% CI, 5-19%) among cases with a matched donor (p=0.003). The cumulative relapse rate at three and five years was 22% (95% CI, 13-31%) and 29% (95% CI, 16-42%), respectively. After a median follow-up of 33 months (range, 12-76 months) five-year estimated disease-free survival (DFS) and OS was 51% (95% CI, 38-64%) and 67% (95% CI, 55-79%), respectively.

A retrospective study analyzed the impact of conditioning intensity on outcomes of allogeneic HCT in patients with myelofibrosis (MF).[41] This multicenter trial included 46 consecutive patients treated at three Canadian and four European transplant centers between 1998 and 2005. Twenty-three patients (median age 47 years, range 31-60 years) underwent myeloablative conditioning, and 23 patients (median age 54 years, range 38-74 years) underwent RIC. The majority in both groups (85%) were deemed intermediate- or high-risk. At a median follow-up of 50 (range 20-89) months, there was a trend for better progression-free survival (PFS) at three years in RIC patients compared to myeloablative-conditioned patients

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(58%, range 23-62 vs. 43%, range 35-76, respectively, p=0.11); there was a similar trend in three-year OS (68%, range 45-84 vs. 48%, range 27-66, respectively, p=0.08). Non-relapse mortality rates at three years trended higher in myeloablative conditioned cases than RIC cases (48%, range 31-74 vs. 27%, range 14-55, respectively, p=0.08). The results of this study suggest that both types of conditioning regimens have curative potential in patients with MF. Despite the RIC patients being significantly older with longer disease duration and poorer performance status than those who received conventional conditioning, the groups had similar outcomes, supporting the use of RIC allogeneic HCT in this population.

In a retrospective study in nine Nordic transplant centers, a total of 92 patients with MF in chronic phase underwent allogeneic HCT.[42] Myeloablative (MA) conditioning was given to 40 patients, and RIC was used in 52 patients. The mean age in the two groups at transplantation was 46±12 and 55±8 years, respectively (p<0.001). When adjustment for age differences was made, the survival of the patients treated with RIC was significantly better (p=0.003). Among the RIC patients, survival was significantly (p=0.003) greater for patients younger than age 60 years (a 10-year survival close to 80%) than for patients older than 60 years. The stem-cell source did not significantly affect the survival. No significant difference was found in NRM at 100 days between the MA- and the RIC-treated patients. The probability of survival at five years was 49% for the MA-treated patients and 59% in the RIC group (p=0.125). Patients treated with RIC experienced significantly less acute GVHD compared with patients treated with MA conditioning (p<0.001). The OS at 5 years was 70%, 59% and 41% for patients with Lille score 0, 1 and 2, respectively (p=0.038, when age adjustment was made). Twenty-one percent of the patients in the RIC group were given donor lymphocyte infusion because of incomplete donor chimerism, compared with none of the MA-treated patients (p<0.002). Nine percent of the patients needed a second transplant because of graft failure, progressive disease or transformation to AML, with no significant difference between the groups.

Gupta reported better disease-free survival rates in a more recent analysis of 233 patients with primary myelofibrosis who underwent RIC HCT from 1997 to 2010.[43] Five-year OS was 47% (95% CI, 40% to 53%). Conditioning regimen was not significantly associated with OS.

In a prospective nonrandomized study, Rondelli compared survival outcomes for reduced intensity allogeneic HCT in patients with sibling donors (n=32) or unrelated donors (n=34).[44] Mean follow-up was 25 months for living patients. All outcomes were significantly superior for the patients with sibling donors. Engraftment occurred in 97% of siblings and 76% of unrelated transplants, with overall graft failure rates of 6% and 36%, respectively. Corresponding OS was 75% and 32%, respectively, and nonrelapse mortality was 22% and 59%, respectively. One limitation of this study is that it did not include data on HLA antibodies which may have influence the rejection rate in the unrelated transplant patients. The authors concluded that more data from large prospective studies are needed to determine if donor match can significantly reduce nonrelapse mortality in high risk allogeneic HCT.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

Current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for myelodysplastic syndromes (MDS; v.1.2020) make the following recommendation about hematopoietic cell transplantation (HCT) in general[45]:

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"For patients who are transplant candidates, an HLA [human leukocyte antigen]-matched sibling or HLA-matched unrelated donor can be considered. Results with HLA-matched, unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC [reduced-intensity conditioning] for HCT is generally the strategy in older individuals."

SUMMARY

Hematopoietic cell transplantation (HCT) is, at present, the only potentially curative treatment option for patients with myelodysplastic syndromes and myeloproliferative neoplasms. The absence of curative therapies coupled with clinical data and the clinical practice guidelines from the National Comprehensive Cancer Network permit the conclusion that allogeneic HCT using either a myeloablative or reduced-intensity conditioning (RIC) regimen may be considered medically necessary in appropriately selected patients with myelodysplastic syndromes and myeloproliferative neoplasms.

There is not enough research to show that the use of allogeneic hematopoietic cell transplantation (HCT) not meeting policy criteria improves health outcomes. Therefore, HCT with or without RIC for the treatment of myelodysplastic syndromes and myeloproliferative neoplasms that does not meet the policy criteria is considered investigational.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38207	Transplant preparation of hemetopoietic progenator cells, cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and

APPENDIX I

2016 World Health Organization (WHO) Classification of MDS

The myeloid neoplasms are categorized according to criteria developed by the WHO.

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APPENDIX I

WHO myeloid neoplasm and acute leukemia classification

Myeloproliferative neoplasms (MPN)
- Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1,* or with *PCM1-JAK2*
- Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
- *Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2*

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)
- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- *Provisional entity: Refractory cytopenia of childhood*

Myeloid neoplasms with germ line predisposition

Acute myeloid leukemia (AML) and related neoplasms
- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*

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APPENDIX I
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy

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APPENDIX I
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.25

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

Effective: April 1, 2020

Next Review: January 2021
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Allogeneic hematopoietic cell transplantation, using myeloablative or reduced-intensity conditioning, may be considered **medically necessary** for selected patients with the following disorders:

A. Hemoglobinopathies
   1. Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage. Factors associated with a high risk of stroke or end-organ damage include: recurrent chest syndrome, recurrent vaso-occlusive crises, red blood cell alloimmunization on chronic transfusion therapy.
   2. Homozygous beta-thalassemia (i.e., thalassemia major)

B. Bone marrow failure syndromes

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1. Hereditary
    a. Inherited aplastic anemia
    b. Fanconi anemia
    c. Dyskeratosis congenita
    d. Shwachman-Diamond
    e. Diamond-Blackfan
2. Acquired
    a. Bone marrow failure syndromes secondary to drug or toxin exposure
    b. Acquired aplastic anemia (i.e., pancytopenia with hypocellular bone marrow)

C. Primary immunodeficiencies (See Policy Guideline #1)
1. Absent or defective T-cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
2. Absent or defective natural killer function (e.g. Chediak-Higashi syndrome)
3. Absent or defective neutrophil function (e.g. Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)

D. Inherited metabolic disorders (See Policy Guideline # 2): Lysosomal and peroxisomal storage disorders, except Hunter, Sanfilippo, and Morquio syndromes

E. Genetic disorders affecting skeletal tissue: Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease)

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

1. IMMUNODEFICIENCIES

The following lists the immunodeficiencies that have been successfully treated by

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allogeneic hematopoietic cell transplantation (HCT)[1]

Lymphocyte immunodeficiencies

Adenosine deaminase deficiency
Artemis deficiency
Calcium channel deficiency
CD 40 ligand deficiency
Cernunnos/X-linked lymphoproliferative disease deficiency
CHARGE syndrome with immune deficiency
Common gamma chain deficiency
Deficiencies in CD 45, CD3, CD8
DiGeorge syndrome
DNA ligase IV
Interleuken-7 receptor alpha deficiency
Janus-associated kinase 3 (JAK3) deficiency
Major histocompatibility class II deficiency
Omenn syndrome
Purine nucleoside phosphorylase deficiency
Recombinase-activating gene (RAG) 1/2 deficiency
Reticular dysgenesis
Winged helix deficiency
Wiskott-Aldrich syndrome
X-linked lymphoproliferative disease
Zeta-chain-associated protein-70 (ZAP-70) deficiency

Phagocytic deficiencies

Chediak-Higashi syndrome
Chronic granulomatous disease
Hemophagocytic lymphohistiocytosis
Griscelli syndrome, type 2
Interferon-gamma receptor deficiencies
Leukocyte adhesion deficiency
Severe congenital neutropenias
Shwachman-Diamond syndrome

Other immunodeficiencies

Autoimmune lymphoproliferative syndrome
Cartilage hair hypoplasia
CD25 deficiency
Hyper IgD and IgE syndromes
ICF syndrome
IPEX syndrome
NEMO deficiency
NF-KB inhibitor, alpha (IKB-alpha) deficiency
Nijmegen breakage syndrome

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2. **INHERITED METABOLIC DISORDERS**

Allogeneic HCT has been proven effective in some cases of:

Alpha-mannosidosis
Aspartylglucosaminuria
Childhood onset cerebral X-linked adrenoleukodystrophy
Globoid-cell leukodystrophy
Hurler Syndrome
Maroteaux-Lamy Syndrome
Metachromatic leukodystrophy
Sly Syndromes,

Allogeneic HCT is possibly effective for:

Farber lipogranulomatosis
Fucosidosis
Galactosialidosis
Gangliosidosis
Gaucher types 1 and 3
GM1
Mucolipidosis II (I-cell disease)
Multiple sulfatase deficiency
Niemann-Pick disease
Neuronal ceroid lipofuscinosis
Sialidosis
Wolman disease.

Allogeneic HCT has not been effective in:

Hunter syndrome
Morquio syndrome
Sanfilippo syndrome[2]

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

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BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in patients who receive myeloablative doses of cytotoxic drugs with or without whole body radiation therapy. Although broadly speaking there are two types of HSCTs, autologous and allogeneic, only allogeneic HSCT is relevant to this discussion. Allogeneic HCT refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic cells and the recipient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

PREPARATIVE CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC HCT

The conventional practice of allogeneic HCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC allotransplantation. They represent a continuum in their intensity, from nearly totally myeloablative, to minimally myeloablative with lymphoablation.

GENETIC DISEASES AND ACQUIRED ANEMIAS

Hemoglobinopathies

The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, reducing oxygen delivery. The supportive treatment of beta-thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic, and endocrine function.[3] The only definitive cure for thalassemia is to correct the genetic defect with allogeneic HCT.

Sickle cell disease is caused by a single amino acid substitution in the beta chain of hemoglobin, and, unlike thalassemia major, has a variable course of clinical severity.[3] Sickle cell disease typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for males and 48 for females. Three major therapeutic options

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are available: chronic blood transfusions, hydroxyurea, and HCT, the latter being the only possibility for cure.[3]

Bone marrow failure syndromes

Aplastic anemia in children is rare, and is most often idiopathic and less commonly due to a hereditary disorder. Inherited syndromes include Fanconi anemia, a rare, autosomal recessive disease, characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently this disease terminates in a myelodysplastic syndrome or acute myelogenous leukemia. Most patients with Fanconi anemia succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age.[4] In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

Dyskeratosis congenita is characterized by marked telomere dysregulation with clinical features of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia.[5] Early mortality is associated with bone marrow failure, infections, pulmonary complications, or malignancy.[5]

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia.[5] Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of myelodysplastic syndrome and malignant transformation, especially acute myelogenous leukemia. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow with 30% of patients also having a variety of physical anomalies.[5]

Primary immunodeficiencies

The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes.[1] The most severe defects (collectively known as severe combined immunodeficiency or SCID) cause an absence or dysfunction of T lymphocytes, and sometimes B lymphocytes and natural killer cells.[1] Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the life span of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood.[1] Bone marrow transplant is the only definitive cure and the treatment of choice for SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function.[6]

Inherited metabolic diseases

Lysosomal storage disorders consist of many different rare diseases caused by a single gene defect, and most are inherited as an autosomal recessive trait.[7] Lysosomal storage disorders are caused by specific enzyme deficiencies that result in defective lysosomal acid hydrolysis of endogenous macromolecules that subsequently accumulate as a toxic substance. Peroxisomal

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storage disorders arise due to a defect in a membrane transporter protein that leads to defects in the metabolism of long-chain fatty acids. Lysosomal storage disorders and peroxisomal storage disorders affect multiple organ systems, including the central and peripheral nervous systems. These disorders are progressive and often fatal in childhood due to both the accumulation of toxic substrate and a deficiency of the product of the enzyme reaction.[7] Hurler syndrome usually leads to premature death by five years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs don't cross the blood-brain barrier, which results in ineffective treatment of the central nervous system. Stem-cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier.[7] The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells, for example microglial cells in the brain and Kupffer cells in the liver.[7]

Allogeneic HCT has been used primarily to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1.[7] The first stem-cell transplant for an inherited metabolic disease was in 1980 in a patient with Hurler syndrome. Since that time, more than 1,000 transplants have been performed worldwide.[7]

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis (MPS)	MPS I	Hurler, Scheie, H-S
	MPS II	Hunter
	MPS III A-D	Sanfilippo A-D
	MPS IV A-B	Morquio A-B
	MPS VI	Maroteaux-Lamy
	MPS VII	Sly
Sphingolipidosis	Fabry's	
	Farber's	Lipogranulomatosis
	Gaucher's I-III	
	GM1 gangliosidosis	
	Niemann-Pick disease A and B	
	Tay-Sachs disease	
	Sandhoff's disease	
	Globoid leukodystrophy	Krabbe disease
	Metachromatic leukodystrophy	MLD
Glycoproteinosis	Aspartylglucosaminuria	
	Fucosidosis	
	alpha-Mannosidosis	
	beta-Mannosidosis	
	Mucolipidosis III and IV	Sialidosis
Other lipidoses	Niemann-Pick disease C	
	Wolman disease	
	Ceroid lipofuscinosis	Type III-Batten disease
Glycogen storage	GSD type II	Pompe
Multiple enzyme deficiency	Galactosialidosis	

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	Mucolipidosis type II	I-cell disease
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

Infantile malignant osteopetrosis

Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow.[8] Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis. Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately six months of age, and severe hematologic malfunction with bone marrow failure. Seventy percent of these patients die before the age of six, often of recurrent infections.[8] HCT is the only curative therapy for this fatal disease.

EVIDENCE SUMMARY

HEMOGLOBINOPATHIES

Sickle Cell Disease (SCD)

Systematic Reviews

In a 2013 Cochrane systematic review, authors determined whether stem cell transplantation improves survival and prevents symptoms and complications associated with sickle cell disease.[9] In addition, authors examined the risks of stem cell transplantation against the potential long-term gain for people with sickle cell disease. Selection criteria was limited to randomized controlled and quasi-randomized studies that compared any method of stem cell transplantation with either each other or with any of the preventive or supportive interventions (e.g. periodic blood transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen) in people with sickle cell disease irrespective of the type of sickle cell disease, gender and setting. Though 10 trials were identified, no trials met the inclusion criteria for the review. Authors conclude that studies on the use of hematopoietic stem cell for treatment of sickle cell disease are limited to observational and other less robust studies. Authors did not identify any randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations. This systematic review identified the need for a multicenter randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in people with sickle cell disease.

Nonrandomized Studies

The use of HCT in patients with sickle cell disease has been well studied over the past decade. Therefore, this section will only summarize the most recent evidence in large to moderate nonrandomized studies and will not include smaller case series.

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Eapen (2019) reported analyses of patients with sickle cell disease and who underwent transplantation.[10] Relative risk based on donor type and conditioning regimen was calculated. Of the 910 total patients, 61% had an HLA-matched sibling donor, 15% had a haploidentical related donor, 12% had a matched unrelated donor, and 11% had a mismatched unrelated donor. Statistically significant differences in event-free survival were reported, with worse outcomes in patients 13 years or older (hazard ratio [HR] 1.74, 95% CI 1.24 to 2·45; p=0.0014), in those who received a transplant from a haploidentical related donor (HR 5.30, 3.17 to 8.86; p<0.0001), matched unrelated donors (HR 3.71, 2.39 to 5.75; p<0.0001), mismatched unrelated donors (HR 4.34, 2·58 to 7.32; p<0.0001), and reduced-intensity conditioning (HR 1.97, 1.15 to 3.36; p=0.013). No significant differences were identified in event-free survival between recipients of transplants from non-sibling donors: haploidentical related donors (HR 1.43, 0.81 to 2.50; p=0.21) or mismatched unrelated donors (HR 1.17, 0.67 to 2.05; p=0.58) versus HLA-matched unrelated donors, mismatched unrelated donors versus haploidentical related donors (HR 1.22, 0.65-2.27; p=0.98), or myeloablative compared with non-myeloablative regimens (HR 1.57, 0.95 to 2.61; p=0.079).

In 2016, Baronciani performed a retrospective study, extracting data from the European Group for Blood and Marrow Transplantation (EBMT) hemoglobinopathy prospective registry database, including 1493 consecutive patients with thalassemia major transplanted between 2000 and 2010. In total, 1359 (91%) HCTs were performed on patients <18 years old, 1061 were from a human leukocyte Ag-identical sibling donor. The two-year overall survival (OS) and thalassemia-free survival were 88 ± 1% and 81 ± 1%, respectively. Transplantation from a human leukocyte Ag-identical sibling offered the best results, with OS and thalassemia-free survival of 91 ± 1% and 83 ± 1%, respectively. No significant differences in survival were reported between countries. The threshold age for optimal transplant outcomes was around 14 years, with an OS of 90 to 96% and a thalassemia-free survival of 83 to 93% when transplants were performed before this age.

In 2016, Nickel conducted a retrospective cohort study of pediatric patients who had HCT for SCD to determine the long –term effect on cell transplantation on splenic function.[11] Overall, more patients had splenic uptake after HCT (34/38 [89%]) than prior to HCT (14/38 [37%]) (p<0.0001). Fifty-three nonsplenectomized Hb SS and $S\beta^0$ -thalassemia patients were assessed by liver-spleen scan at a median of 2.0 years post-HCT, and 8/53 (15%) had normal, 40/53 (75%) decreased, and 5/53 (9%) absent splenic uptake. However, older patient age at time of HCT and extensive chronic GVHD appear to be risk factors for poor post-HCT splenic function.

In 2015 Bhatia measured health-related quality of life (HRQoL) before and after allogeneic HCT by assessing physical, psychological, and social functioning in patients younger than 21 years of age with sickle cell disease (SCD) who have undergone reduced-toxicity conditioning followed by HCT (n=17).[12] Data was collected before transplantation and on days 180 and 365 post-transplantation, and the change in HRQoL from baseline was assessed. In the patient-reported analysis adjusted for demographic and medical variables, the estimated improvements in overall HRQoL were 4.45 (p = 0.380) and 16.58 (p = 0.003) at 180 and 365 days, respectively, after transplantation.

In a 2014 report, 30 patients aged 16 to 65 years with severe sickle cell phenotype enrolled in a RIC allogeneic HCT study consisting of alemtuzumab (1 mg/kg in divided doses), total body irradiation (300 cGy), sirolimus, and infusion of unmanipulated filgrastim mobilized peripheral blood stem cells from HLA-matched siblings.[13] The primary end point was treatment success

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at one year after the transplant, defined as a full donor-type hemoglobin for patients with sickle cell disease and transfusion independence for patients with thalassemia. Secondary end points included the level of donor leukocyte chimerism; incidence of acute and chronic GVHD; and sickle cell-thalassemia disease-free survival (DFS), immunologic recovery, and changes in organ function. Twenty-nine patients survived a median 3.4 years (range, 1 to 8.6), with no nonrelapse mortality. One patient died from intracranial bleeding after relapse. The normalized hemoglobin and resolution of hemolysis among engrafted patients were accompanied by stabilization in brain imaging, a reduction of echocardiographic estimates of pulmonary pressure, and allowed for phlebotomy to reduce hepatic iron. A total of 38 serious adverse events were reported: pain and related management, infections, abdominal events, and sirolimus-related toxic effects.

Most of the experience with allogeneic HCT and sickle cell disease comes from three major clinical series[3] which were included in the review process of the 2013 Cochrane review described above but did not meet inclusion criteria. The largest series to date consisted of 87 symptomatic patients, the majority of whom received donor allografts from siblings who are human leukocyte antigen (HLA) identical. The results from this series[14] and the other two[15,16] were similar, with overall survival rates ranging from 92% to 94% and event-free survival from 82% to 86% with a median follow-up ranging from 0.9 to 17.9 years.[3]

Beta-Thalassemia

More than 3,000 patients worldwide have been treated for beta-thalassemia with allogeneic HCT.[3] Overall survival rates have ranged from 65% to 100% and thalassemia-free survival up to 73%.[3] The Pesaro risk stratification system classifies patients with thalassemia who are to undergo allogeneic HCT into risk groups I through III on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with two risk factors, and III with all 3).[17] The outcome of allogeneic HCT in over 800 patients with thalassemia according to risk stratification has shown overall and event-free survival of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III.[17]

Systematic Reviews

A 2014 Cochrane systematic review evaluated the safety and effectiveness of different types of allogeneic HCT in subjects with transfusion-dependent beta-thalassemia major (homozygous beta-thalassemia), beta-thalassemia intermedia, or beta0/+-thalassemia variants requiring chronic blood transfusion.[18] Selection criteria were limited to randomized controlled and quasi-randomized studies that compared allogeneic HCT with each other or with standard therapy (i.e., regular transfusion and chelation regimen). No studies were identified that met these inclusion criteria. Some limited data have become available the last few years in nonrandomized trials comparing conditioning regimens, different risk groups, outcomes with different donor sources, various myeloablative treatments, and outcomes with HLA matched or related and unrelated donors. However, the authors concluded that questions related to the safety and efficacy of different types of stem cell transplantation remain unanswered.

Nonrandomized Studies

The use of HCT in patients with beta-thalassemia has been well studied over the past decade. Therefore, this section will only summarize the most recent evidence in large to moderate nonrandomized studies and will not include smaller case series.

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A single-center case control study of HCT for thalassemia was published by Caocci in 2017.[19] A cohort of 258 children and adult patients treated with HCT was compared with a randomly selected group of 258 age and sex matched conventionally treated patients. Of the HCT-treated patients, 67% underwent sibling HCT and 33% had unrelated donors. Ninety-seven patients were 16 years or older. Grade II-IV acute and chronic graft versus host disease occurred in 23.6% and 12.9%, respectively, while probability of rejection was 6.9%. Transplant-related mortality was 13.8%. Median follow-up was 11 years, with a range of 1 to 30 years. The 30-year OS was calculated to be 82.6% in HCT-treated patients and 85.3% in conventionally-treated patients. These values were not significantly different. In HCT-treated patients, 30-year thalassemia-free survival was calculated to be 77.8%.

A 2015 report on 489 patients with non-malignant hematologic disorders who underwent allogeneic HCT between May 1997 and April 2012 included 152 patients with β-thalassemia.[20] There were 92 males and 50 females and mean age at transplantation was 5.7 years (range 1.1 to 23 years). At the time of transplantation, twenty-six patients (17%) had Pesaro class I, 103 (68%) had class II and 23 (15%) had class III. 132 patients received peripheral blood stem cells and 20 received bone marrow grafts. Mean times to neutrophil and platelet engraftment were 21.4 days (8 to 69) and 32.8 days (7 to 134), respectively. The incidence of graft rejection was significantly lower in patients who received peripheral blood stem cells than in those who received bone marrow grafts (9% vs 25%) (p=0.036). Acute GVHD grade II–IV occurred in 15% while chronic GVHD occurred in 12% of the whole group of patients. The incidence of transplant related mortality for the whole group was 18%. After a median follow-up period of 12 years, the OS of the whole group of patients was 82.4%. DFS of the whole group of patients was 72.4% [74% in the peripheral blood stem cell transplantation group compared to 64% in the bone marrow stem cell transplantation group (p=0.381)], which may be attributed to the higher incidence of graft rejection in bone marrow groups.

Bernardo (2012) reported the results of 60 thalassemia patients (median age, seven years; range, 1 to 37) who underwent allogeneic HCT after a reduced-intensity conditioning regimen based on the treosulfan.[21] Before transplant, 27 children were assigned to risk class 1 of the Pesaro classification, 17 to class 2, and four to class 3; 12 patients were adults. Twenty patients were transplanted from an HLA-identical sibling and 40 from an unrelated donor. The cumulative incidence of graft failure and transplantation-related mortality was 9% and 7%, respectively. Eight patients experienced grade II-IV acute GVHD, the cumulative incidence being 14%. Among 56 patients at risk, one developed limited chronic GVHD. With a median follow-up of 36 months (range, 4 to 72), the five-year probability of survival and thalassemia-free survival were 93% and 84%, respectively. Neither the class of risk nor the donor used influenced outcome.

In a 2014 report on RIC HCT, 98 patients with class 3 thalassemia were transplanted with related or unrelated donor stem cells.[22] Seventy-six of the patients age 10 years or younger received a conventional myeloablative conditioning regimen (cyclophosphamide [Cy], busulfan, + fludarabine [Flu]). The remaining 22 patients, who were older than 10 years, had hepatomegaly and in several instances additional comorbidity problems, underwent HCT with a novel RIC regimen (fludarabine and busulfan). EFS (86% vs 90%, respectively), and OS (95% vs 90%, respectively) were not significantly different between the groups. However, a higher incidence of serious treatment-related complications was observed in the myeloablative conditioned group. Further, graft failures occurred in six patients in the myeloablated group (8%), but none occurred in the RIC group.

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Reduced-intensity Conditioning (RIC)

Experience with reduced-intensity preparative regimens and allogeneic HCT for the hemoglobinopathies is limited to a small number of patients. In adult patients, severe GVHD has been observed with the use of RIC regimens.[23] Challenges with high rates of graft rejection (10% to 30%) may be due to hemoglobinopathy patients possibly being allosensitized due to repeated blood transfusions and, as opposed to cancer patients who may undergo RIC allogeneic transplants, patients with hemoglobinopathies have received no prior immunosuppressive therapies and may even have significant bone marrow hyperplasia.[17]

BONE MARROW FAILURE SYNDROMES

Fanconi Anemia (FA)

In Fanconi anemia (FA), bone marrow transplant is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HCT, with cure of the marrow failure and amelioration of the risk of leukemia.[4]

Nonrandomized Studies

In 2015, Kuşkonmaz reported on the outcomes of 26 patients with FA who underwent HCT using fludarabine (Flu) based conditioning regimen at a single center from 2004 to 2014.[24] The median age of the patients at the time of transplantation was 9.6 years (range 5.6 to 17.0 years). Donors were (HLA)-identical siblings in 18 patients, HLA-identical other relatives in six patients, and HLA 1-antigen mismatched sibling in two patients. Twenty-five patients had successful engraftment, and one developed poor graft function and underwent a second HCT. Acute GVHD (≥grade 2) occurred in two patients (7.6%) and chronic GVHD in one patient (3.9%). Three patients developed venoocclusive disease (11.5%). Survival rate was 96.2% (25/26) at a median follow-up of 54 months (10 to 131 months). Although none of the patients developed secondary malignancy during the follow-up period, the follow-up period was too short to estimate this risk.

In 2015, Ristano published on an Italian FA registry, including over 180 patients, more than half which (102 out of 180, 57%) had received a HCT from either a non-affected sibling or matched unrelated donor.[25] The incidence of all solid cancers and of head and neck tumors was not statistically different between patients who had received a HCT and those who had not (p=0.43 and p=0.50, respectively), however the analysis is limited by the small number of events. In HCT patients the majority of deaths were related to treatment complications such as infections (n=11, 25.5% of total deaths in HCT patients), GVHD (n=11, 25.5%) and other transplant related mortality (TRM) (n=13, 30%). Solid tumors accounted for 9% of deaths (n=4).

In a 2008 study of allogeneic HCT from matched related donors over six years in Fanconi anemia, totaling 103 patients, overall survival ranged from 83% to 88% with transplant-related mortality ranging from 8% to 18.5% and average chronic graft-versus-host disease (GVHD) of 12%.[26]

In an attempt to improve outcomes for alternative donor HCT for FA patients, MacMillan added fludarabine (FLU), to the conditioning regimen for 130 FA patients that were treated between 1995 and 2012, with median follow-up times between 4 to 18 years. The addition of FLU enhanced engraftment three-fold, and in regression analysis, recipients of FLU-containing

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regimens had a lower risk of mortality at five years. The European Group for Blood and Marrow Transplantation (EBMT) working party has analyzed the outcomes using alternative donors in 67 patients with Fanconi anemia. Median two-year survival was 28 + 8%.[5] Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year overall survival rates were 13% and 52% in patients who received non-fludarabine versus fludarabine-based regimens.[5]

Zanis-Neto (2005) reported the results of 30 patients with Fanconi anemia treated with reduced-intensity conditioning (RIC) regimens, consisting of low-dose cyclophosphamide.[27] Seven patients were treated with cyclophosphamide at 80 mg/kg and 23 with 60 mg/kg. Grade 2-3 acute GVHD rates were 57% and 14% for patients who received the higher and lower doses, respectively (p=0.001). Four of the seven patients who received the higher dose were alive at a median of 47 months (range: 44 to 58), and 22 of 23 given the lower dose were alive at a median of 16 months (range: 3 to 52). The authors concluded that a lower dose of cyclophosphamide conditioning had lower rates of GVHD and was acceptable for engraftment.

In a retrospective study of 98 unrelated donor transplantations for Fanconi anemia reported to the CIBMTR, Wagner reported that fludarabine-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved three-year overall survival (OS) (52% vs. 13%, respectively; p<0.001) compared with nonfludarabine regimens.[28]

Acquired Severe Aplastic Anemia (SAA)

Systematic Reviews

A 2014 Cochrane systematic review evaluated the effectiveness and adverse events of first-line allogeneic HCT of human leucocyte antigen (HLA)-matched sibling donors (MSD) compared with first-line immunosuppressive therapy (IST) for acquired severe aplastic anemia (SAA).[29] Selection criteria included participants with newly diagnosed severe SAA in RCTs or prospective non-RCTs. Three studies met inclusion criteria; the studies were conducted between 1976 and 1997.[30-32] Thus, these data were collected more than 15 years ago. All three studies were rated as high risk for bias due to the study design. The meta-analysis showed no statistically significant difference in overall mortality between MSD-HCT (n=121) and IST (n=181), with overall survival (OS) ranging from 45% to 84% and 45% to 87%, respectively. However, treatment-related mortality in the MSC-HCT group ranged from 20% to 42%. Graft failure rate were variable and caused death in 3% to 16% of transplanted patients. GVHD affected 25-50% of transplanted patients.

One of these studies included in the review, by Bayever (1984),[30] reported 92% of patients in the MSD-HCT group had a Karnofsky Performance Status higher than 70% compared to less than 50% of the IST group participants. Secondary clonal disease or malignancies were rare in both groups. The authors noted that a 2008 article[33] reported improved outcomes since 1996 for HCT but not for IST, possibly attributable to detailed HLA-matching and less irradiation-based conditioning. Limitations of this systematic review included the data being 15 or more years old and therefore not applicable to current standard care. The use of Mendelian randomization requiring HLA-matched sibling donor did not necessarily minimize bias since patients with large families had a greater chance of finding a donor and thus being assigned to the HCT group than patients with fewer siblings. In addition, the testing of multiple siblings as

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potential donors may delay assignment and treatment compared with patients with no siblings who could be assigned immediately and thus were at earlier risk for adverse events. The authors concluded that insufficient and biased data did not permit conclusions about the comparative effectiveness of MSD-HCT and IST.

Nonrandomized Studies

Small case series have been published that focus on children with SAA that do not have a matched sibling donor, thereby requiring either an unrelated or unmatched donor. The goal of these case series is to optimize the conditioning regimes and therapeutic strategies for these children in order to improve transplantation success (engraftment) and improved health outcomes like overall survival.

Nqwube (2015) performed a small prospective multi-center HCT trial in 17 children with SAA using a novel reduced-intensity conditioning (RIC) regimen with alemtuzumab, fludarabine and melphalan, and the best available donor. Eight transplants were from related donors, and nine were from unrelated donors, matched at 7-8/8 loci, with follow-up times ranging from 6 to 128 months.[34] Unrelated donors and related donors were assessed separately for overall survival and event free survival, with OS being 78% and 100% when donors were unrelated and related, respectively. For all other transplant outcomes, these two groups were analyzed together. Overall, treatment related mortality was 12% and the incidence of acute graft-versus-host disease was between 18 and 29%. At two years, 92% of patients had discontinued immunosuppression successfully.

Esteves (2015) recently followed 16 SAA patients who underwent haploidentical transplantation using a RIC regimen with post-transplant treatment with cyclophosphamide (Cy).[35] The rate of neutrophil engraftment was 94% and of platelet engraftment was 75%. Two patients had secondary graft failure and were successfully salvaged with another transplant. Three patients developed acute GVHD and the one-year OS was 67.1%.

In 2015, the European Group for Blood and Marrow Transplantation (EBMT) working party analyzed the outcomes of 563 children with SAA (up to 12 years old), comparing those treated with matched family donor (MFD) (HCT (n=396) or immunosuppressive treatment (IST)(n=167).[36] There was no significant difference between HCT and IST in terms of OS (91% and 87%, respectively), but EFS was significantly higher in the HCT group (87% vs. 33% (p=0.001). Of the 167 initially treated with IST, 91/167 (55%) failed front-line IST and were successfully rescued after HCT, with an OS of 83%. The OS and EFS rates reported in this age group of children with SAA are superior to those reported for adolescents (12 to 18 years old) with SAA who have undergone HCT versus IST.[37] In adolescents, OS was 86% in the HCT group and 90% in patients given front-line IST alone and EFS was 83% and 64%. Both of these studies indicated that HCT, using a matched family donor is the first-choice treatment.

In 2012, a randomized Phase III trial compared two different conditioning regimens in high-risk aplastic anemia patients (n=79) who underwent allogeneic HCT.[38] Patients in the cyclophosphamide (Cy) plus anti-thymocyte globulin (ATG) arm (n=39) received Cy at 200 mg/kg; those in the Cy-fludarabine (Flu)-ATG group (n=40) received Cy at 100 mg/kg and Flu at 150 mg/m^2 (NCT01145976). No difference in engraftment rates was reported between arms. Infection with an identified causative organism and sinusoidal obstruction syndrome, hematuria, febrile episodes, and death from any cause tended to be more frequent in the Cy-ATG arm but did not differ significantly between arms. Overall survival at four years did not

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differ between the Cy-ATG and Cy-Flu-ATG arms (78% vs. 86%, respectively, p=0.41). Although this study was reported to be underpowered by authors to detect real differences between the conditioning regimens, the results suggest an RIC regimen with Cy-Flu-ATG appears to be as safe as a more traditional myeloablative regimen comprising Cy-ATG in allogeneic HCT.

Dyskeratosis Congenita

Results with allogeneic HCT in dyskeratosis congenita have been disappointing due to severe late effects, including diffuse vasculitis and lung fibrosis.[5] Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results are available at this time.[5]

Nonrandomized Studies

In 2013, outcomes after allogeneic HCT were reported in 34 patients with dyskeratosis congenita who underwent transplantation between 1981 and 2009.[39] The median age at transplantation was 13 years (range, 2 to 35). Approximately 50% of transplantations were from related donors. The day-28 probability of neutrophil recovery was 73% and the day-100 platelet recovery was 72%. The day-100 probability of grade II to IV acute GVHD and the three-year probability of chronic GVHD were 24% and 37%, respectively. The 10-year probability of survival was 30%; 14 patients were alive at last follow-up. Ten deaths occurred within four months from transplantation because of graft failure (n=6) or other transplantation-related complications; nine of these patients had undergone transplantation from mismatched related or from unrelated donors. Another 10 deaths occurred after four months; six of them occurred more than five years after transplantation, and four of these were attributed to pulmonary failure. Transplantation regimen intensity and transplantations from mismatched related or unrelated donors were associated with early mortality. Transplantation of grafts from HLA-matched siblings with Cy-containing nonradiation regimens was associated with early low toxicity. Late mortality was attributed mainly to pulmonary complications and likely related to the underlying disease.

Shwachman-Diamond Syndrome

Experience with allogeneic HCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease.[5]

Nonrandomized Studies

Cesaro (2005) reported 26 patients with Shwachman-Diamond syndrome from the European Group for Blood and Bone Marrow Transplantation registry given HCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myelogenous leukemia (MDS-AML) (n=9); or another diagnosis (n=1).[40] Various preparative regimens were used; most included either busulfan (54%) or total body irradiation (23%) followed by an HLA-matched sibling (n= 6), mismatched related (n=1), or unrelated graft (n=19). Graft failure occurred in five (19%) patients, and the incidence of grade III to IV acute and chronic GVHD were 24% and 29%, respectively. With a median follow-up of 1.1 years, OS was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS-AML or use of total body irradiation–based conditioning regimens were factors associated with a poorer outcome.

Diamond-Blackfan Anemia

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Nonrandomized Studies

In Diamond-Blackfan anemia, allogeneic HCT is an option in corticosteroid-resistant disease.[5] In a report from the Diamond-Blackfan anemia registry, 20 of 354 registered patients underwent allogeneic HCT, and the five-year survival rates were 87.5% if recipients received HLA-identical sibling grafts, but poor in recipients of alternative donors.[5] The CIBMTR reported the results in 61 patients who underwent HCT between 1984 and 2000.[41] Sixty-seven percent of patients were transplanted with an HLA-identical sibling donor. Probability of overall survival after transplantation for patients transplanted from an HLA-identical sibling donor (versus an alternative donor) was 78% versus 45% [p=.01] at one year and 76% versus 39% [p=.01] at three years, respectively.

Severe Congenital Neutropenia

Allogeneic HCT is the only curative treatment of severe congenital neutropenia (SCN).

Nonrandomized Studies

Fioredda (2015) recently published a report on the outcome of 136 SCN patients who underwent HCT between 1990 and 2012 in European and the Middle East.[42] The three-year overall survival (OS) was 82%, and transplant-related mortality (TRM) was 17% in this population. In multivariate analysis, transplants performed at a young age (<10 years), in recent years (after 2000), and from HLA-matched donors were associated with a significantly better OS. Whether the donors were related or unrelated made no difference on overall survival. Frequency of graft failure was 10%. Incidence of acute graft-versus-host disease (GVHD) grade 2-4 was 21% and chronic GVHD was 20%. In multivariate analysis, HLA-matched related donor and prophylaxis with cyclosporine A and methotrexate were associated with lower occurrence of acute GVHD. No secondary malignancies were observed after a median follow-up of 4.6 years.

PRIMARY IMMUNODEFICIENCIES

Nonrandomized Studies

In 2017, Ngwube reported a case series of HCT for Wiskott-Aldrich syndrome.[43] The authors performed a retrospective chart review of twelve patients with a median age of 10.5 months. All patients received allogeneic HCT. Median time to neutrophil and platelet engraftment was 19 and 18.5 months, respectively. At a median follow-up of 67 months, OS was 92%. Grade IV acute graft-versus-host disease occurred in two patients. At day +180, five patients (42%) had mixed donor chimerism. Of those patients, two had full donor chimerism after receiving a second transplant with the same donor, two patients had normalization of the platelet count despite the mixed chimerism, and at the time of publication, one patient remained transfusion dependent awaiting a second transplant.

Norman published a single center case series of HCT for primary immunodeficiency syndrome in 2017.[44] Twenty-two patients received HCT over five years for a variety of primary immunodeficiency syndromes, including severe combined immunodeficiency, chronic granulomatous disease and familial haemophagocytic lymphohistiocytosis. Of these cases, reduced intensity or reduced toxicity conditioning was used in 91%. Donors were unrelated in 75% of cases. Transplant related mortality was 9.5% (calculated at day +100) and there were three total mortalities. Cumulative OS was 86%.

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Fox (2017) reported a case series of 29 adult patients receiving allogeneic HCT for primary immunodeficiencies.[45] All patients received reduced intensity conditioning. There were 18 unrelated donors and 11 related donors. Transplant related mortality occurred in four cases over a median follow-up of 3.5 years. No early or late rejection was observed. OS at three years was 85.2%. Stable mixed chimerism or full donor chimerism was observed in all patients.

In 2016, Patirolgu reported on a retrospective study describing the outcomes of HCTs performed at a single center for primary immunodeficiency diseases in 20 patients at a single center from 2010 to 2015.[46] There was a mixed patient population addressed in this study, with one of nine different conditions, including severe combined immunodeficiency, hemophagocytic lymphohistiocytosis, chronic granulomatous disease, type 2 Griscelli syndrome, B-cell deficiency plus bone marrow failure, severe congenital neutropenia, X-linked lymphoproliferative disease, T-cell deficiency plus relapsed non-Hodgkin lymphoma, and type 1 leukocyte adhesion deficiency. Of the 20 patients, 11 received related HLA-matched, six received haploidentical, two received unrelated HLA-matched, and one received HLA-mismatched transplant. The median age at transplant was 21 months, and median follow-up was five months. Overall survival rate was 65%. Mean engraftment times for neutrophils and platelets were 14.25 ± 3.08 and 24.7 ± 11.4 days. GVHD was observed in 30% of patients.

In 2015, Umeda reported on the clinical outcomes of allogeneic HCT in a retrospective analysis of eight patients with Chediak-Higashi syndrome (CHS), with analysis performed on the remaining six patients still alive.[47] Four of five patients transplanted with myeloablative conditioning had successful engraftment but only three survived, while all three patients transplanted with RIC had successful engraftment and survive long term. Despite the engraftment success in both groups, the authors report that it is too early to tell if the post-transplant neurological deficits reported by other groups on patients with CHS will develop.

In 2015, Allewelt conducted a retrospective analysis of seven patients who underwent allogeneic HCT at a single center for HIGM syndrome with CD40 ligand deficiency.[48] Median age at transplant was 5.2 years (range 0.7 to 19.3). Five patients received myeloablative conditioning, and two patients received reduced intensity conditioning. Post-transplantation complications included veno-occlusive disease, hemorrhagic cystitis, adenoviremia, and cryptosporidium recurrence in one patient each. Two patients developed acute GVHD grades II-IV that resolved promptly with treatment and none developed extensive chronic GVHD. All patients were alive at a median follow-up of 9.7 (range 9.7 to 16.1) years post-transplantation with predominantly donor chimerism and no recurrent infections. HCT results in excellent survival and sustained immune reconstitution in patients with CD40 ligand deficiency using both myeloablative and reduced intensity conditioning approaches and various graft sources, including bone marrow, peripheral blood, and umbilical cord blood.

A prospective study in 16 centers in 10 countries worldwide enrolled patients aged 0 to 40 years with chronic granulomatous disease (CGD) treated with RIC HCT consisting of high-dose Flu, serotherapy or low-dose alemtuzumab, and low-dose (50% to 72% of myeloablative dose) or targeted busulfan administration.[49] Unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related-donors or HLA-9/10 or HLA-10/10 matched unrelated-donors were infused. The primary end points were OS and EFS, probabilities of OS and EFS at two years, incidence of acute and chronic GVHD, achievement of at least 90% myeloid donor chimerism, and incidence of graft failure after at least six months of follow-up. A total 56 patients (median age 12.7 years) with chronic granulomatous disease were enrolled; 42

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patients (75%) had high-risk features (i.e., intractable infections and autoinflammation), 25 (45%) were adolescents and young adults (age 14 to 39 years). Median time to engraftment was 19 days for neutrophils and 21 days for platelets. At median follow-up of 21 months, OS was 93% (52/56) and EFS was 89% (50/56). The two-year probability of OS was 96% (95% confidence interval [CI], 86.46 to 99.09) and of EFS was 91% (79.78 to 96.17). Graft-failure occurred in 5% (3/56) of patients. The cumulative incidence of acute GVHD of grade III to IV was 4% (2/56) and of chronic GVHD was 7% (4/56). Stable (>/=90%) myeloid donor chimerism was documented in 52 (93%) surviving patients.

Outcomes of HCT in patients with chronic granulomatous disease (CGD) were compared with those in patients with CGD who were given conventional treatment.[50] Forty-one patients in Sweden were diagnosed with CGD between 1990 and 2012. From 1997 to 2012, 14 patients with CGD, aged 1 to 35 years, underwent HCT and received grafts either from an HLA-matched sibling donor or a matched unrelated donor. Thirteen of the 14 (93%) transplanted patients were reported alive and well at publication. The mean age at transplantation was 10.4 years, and the mean survival time was 7.7 years. In contrast, 7of 13 men or boys with X-linked CGD who were treated conventionally died from complications of CGD at a mean age of 19 years, while the remaining patients suffered life-threatening infections.

Hassan (2012) reported a multicenter retrospective study, which analyzed the outcome of HCT in 106 patients with adenosine deaminase deficient-SCID who received a total of 119 transplants.[51] HCT from matched sibling and family donors had significantly better OS (86% and 81%) in comparison to HCT from matched unrelated (66%; $p<0.05$) and haploidentical donors (43%; $p<0.0001$). Superior OS was also seen in patients who received unconditioned transplants in comparison to myeloablative procedures (81% vs. 54%; $p<0.003$) although in unconditioned haploidentical donor HCT, non-engraftment was a major problem. Long term immune recovery showed that regardless of transplant type, overall T cell numbers were similar although a faster rate of T cell recovery was observed following matched sibling and family donor HCT. Humoral immunity and donor B cell engraftment was achieved in nearly all evaluable surviving patients and was seen even after unconditioned HCT.

HCT using HLA-identical sibling donors can provide correction of underlying primary immunodeficiencies such as severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies in approximately 90% of cases.[1,52] According to a European series of 475 patients collected between 1968 and 1999, survival rates for SCID were approximately 80% with a matched sibling donor, 50% with a haploidentical donor, and 70% with a transplant from an unrelated donor.[52] Since 2000, overall survival for patients with SCID who have undergone HCT is 71%.[1]

Moratto retrospectively reported the long-term outcome and donor cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HCT in the period 1980-2009.[53] Overall survival was 84.0% and was even higher (89.1% five-year survival) for those who received HCT since the year 2000, reflecting recent improvement in outcomes after transplantation from mismatched family donors and for patients who received HCT from an unrelated donor at older than five years. Patients who went to transplantation in better clinical condition had a lower rate of post-HCT complications. Retrospective analysis of lineage-specific donor cell engraftment showed that stable full donor chimerism was attained by 72.3% of the patients who survived for at least one year after HCT. Mixed chimerism was associated with an increased risk of incomplete reconstitution of lymphocyte counts and post-HCT autoimmunity, and myeloid donor cell chimerism < 50% was associated with persistent thrombocytopenia.

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For Wiskott-Aldrich syndrome, an analysis of 170 patients transplanted between 1968 and 1996 demonstrated the impact of donor type on outcomes.[54] Fifty-five transplants were from HLA-identical sibling donors, with a five-year probability of survival of 87% (95% confidence interval [CI]: 74 to 93%); 48 were from other relatives, with a five-year probability of survival of 52% (37 to 65%); and 67 were from unrelated donors with a five-year probability of survival of 71% (58% to 80%; p=.0006).

For patients with genetic immune/inflammatory disorders such as hemophagocytic lymphohistiocytosis, the current results with allogeneic HCT are 60%–70% five-year disease-free survival. For patients with other immunodeficiencies, overall survival rates are 74%, with even better results (90%) with well-matched donors for defined conditions such as chronic granulomatous disease.[1]

X-linked lymphoproliferative disease type 1 (XLP1) is a rare, deadly immune deficiency caused by mutations in SH2D1A.[55] Allogeneic HCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these patients. A recent study reported an eight-year single-center experience. Sixteen consecutive patients diagnosed with XLP1 underwent allogeneic HCT between 2006 and 2013 after an RIC regimen consisting of alemtuzumab, Flu, and melphalan. Fourteen of 16 patients received 8/8 HLA-matched unrelated or related bone marrow grafts, whereas two patients received mismatched unrelated grafts. All patients had hematopoietic recovery. No cases of hepatic veno-occlusive disease or pulmonary hemorrhage were reported. One patient (6%) developed acute GVHD and later also developed chronic GVHD (6%). Five patients (31%) developed mixed chimerism. One-year survival estimated by Kaplan-Meier analysis was 80%, with long-term survival estimated at 71%. There were no occurrences of lymphoma after HCT.

Reduced-intensity Conditioning

Studies so far indicate that RIC regimens may have an important role in treating patients with primary immunodeficiency.[56] In the absence of prospective or larger registry studies, it is not possible to prove superiority of RIC in more stable patients with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae, e.g., infertility and growth retardation, may be avoided or reduced. Currently, RIC HCT using unrelated donors may offer a survival advantage in patients with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (older than five years of age), and chronic granulomatous disease with ongoing inflammatory or infective complications. Minimal intensity conditioning HCT may be particularly suited to unrelated donor HCT in young SCID patients with significant comorbidities.

INHERITED METABOLIC DISORDERS

In the past 25 years, HCT has been performed in about 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders.[7] The majority (>80%) have been in patients with mucopolysaccharidosis I (MPS I; Hurler syndrome), other MPS syndromes (MPS II, MPS III A and B, MPS VI), adrenoleukodystrophy, metachromatic leukodystrophy, and globoid leukodystrophy.[7] With the exception of Hurler and globoid cell leukodystrophy, most published data are single case reports or small series with short follow-up.[57] The benefit of allogeneic HCT appears limited to select subsets of patients with few types of lysosomal storage diseases, and is not effective in patients who have developed overt neurological symptoms or in those with aggressive infantile forms.[57]

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Mucopolysaccharidosis Syndromes

Hurler Syndrome (MPS I)

Impressive results have been observed with allogeneic HCT in Hurler syndrome, which has been performed in these patients for more than 30 years. The benefits that have been observed include improvement of neurocognitive functioning, joint integrity, motor development, linear growth, corneal clouding, cardiac function, and others.[7]

Nonrandomized Studies

In 2016, Ghosh reported on 10 years of experience using enzyme replacement therapy pre-HCT in two pediatric metabolic and transplant centers.[58] Of the 81 patients who underwent a first transplant procedure for Hurler, 88% (71/81) survived and 81% (66/81) were alive and engrafted at a median follow-up of 46 months (range 3 to 124 months). Overall survival and EFS in our cohort were 86% and 80% respectively. The incidence of grade II-IV acute and any chronic GVHD was 17% and 11% respectively. Urinary glycosaminoglycans were significantly reduced after a period of enzyme replacement therapy, and further reductions were seen at 13-24 months and >24 months post-transplantation. In several individuals with decreased cardiac contractility, an improvement of their condition during enzyme replacement therapy enabled them to undergo transplantation. Combined ERT and HCT appears to be the standard of care for patients with Hurler syndrome at many centers.

In 2015, an evaluation of survival and graft outcomes of 62 patients with mucopolysaccharidosis I –IV that have received HCT since 2005, indicate that these patients have high OS (95.2%) and EFS (90.3%) with only low percentages of 13.3% acute graft-versus-host disease (GVHD) and 14.8% chronic GVHD.[59]

A retrospective analysis of 217 Hurler syndrome patients from a large international multi-center study that successfully underwent HCT were assessed at a median of 9.2 years post-transplantation for predictors of long-term outcome.[60] The primary endpoints assessed were neurodevelopmental outcomes and growth. The investigators reported considerable residual disease burden in the majority of the transplanted patients, with high variability between patients. The major predictors of neurodevelopment were the preservation of cognitive function at the time of transplant, and a younger age at transplantation. Normal α-l-iduronidase enzyme level obtained posttransplantation was another highly significant predictor for superior long-term outcome in most organ systems. Other factors that improved long-term outcomes included using exclusively noncarrier donors and achieving complete donor chimerism.

Experience with allogeneic HCT and a reduced-intensity preparative regimen has been reported in seven patients with Hurler syndrome.[61] Six of the patients received transplants from unrelated donors and one received the transplant from a sibling. All patients had initial donor engraftment at 100 days, and there were no reports of severe acute GVHD. Six of the seven children were alive at a median of 1,014 days (range: 726 to 2,222 days) post-transplant.

Survival of engrafted Hurler syndrome patients has been radically changed from that of untransplanted patients, with long-term survival data indicating that life span will be extended many decades.[2] An analysis of nearly 150 transplanted patients with Hurler syndrome showed an overall survival rate of more than 80%.[62]

Hunter Syndrome (MPS II)

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Hunter syndrome (MPS II) is composed of two distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged life span, minimal to no central nervous system involvement, and a slow progression.[2] Experience with allogeneic HCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly.[2] Some authors suggest that HCT would not be justifiable in the attenuated form, because the risks outweigh the possible benefits.[2]

Nonrandomized Studies

Eight patients with Hunter syndrome received an allogeneic HCT between the ages of 3 and 16 years.[63] In six cases, the donor was a sibling with identical HLA status, in one case, the donor was unrelated HLA-compatible, and in one case, the donor was a mismatched unrelated donor. The severity of disease prior to transplant was rated by assessing the age at diagnosis, behavior, and intelligence quotient (IQ) at the time of graft and genotype. Five patients were considered to have severe CNS involvement (i.e., diagnosis before the age of four years and an IQ less than 80), two were considered to have the attenuated form (i.e., diagnosis at five years and normal IQ), and one as intermediate (i.e., diagnosis after the age of four and IQ between 80 and 90). After follow-up ranging from 7 to 17 years, all were still alive with the exception of one patient who died of unrelated causes. Successful engraftment was achieved in all patients and cardiovascular abnormalities stabilized in all patients, hepatosplenomegaly resolved, and joint stiffness improved. Perceptual hearing defects remained stable, and transmission hearing defects improved. Neuropsychological outcome was variable: the two patients with the attenuated phenotype reached adulthood with normal IQ, social and scholastic development, and no language impairment. Four patients with the severe form of the syndrome deteriorated after the graft, and their IQ/developmental quotient had declined below 50 at the time of the last evaluation. Of the patients with the severe form, three lost the ability to walk in their early teens, two lost language at 9 and 11 years, and two developed epilepsy. The remaining two patients with the severe form required special schooling and had poor social and language skills.

Other Mucopolysaccharidosis Syndromes

Nonrandomized Studies

Experience with allogeneic HCT in patients with MPS III (Sanfilippo syndrome) has also been disappointing, with no alteration in the course of neuropsychologic deterioration seen in these patients.[2] The literature addressing the use of HCT in Sanfilippo disease consists of two case reports.[64,65] Vellodi (1992) reported the outcomes of twin girls diagnosed with MPS III who underwent allogeneic HCT and were followed up for nine years.[64] At the time of transplant, both girls were functioning in the low average range of intellectual development. Over the next eight years, both girls had a steady decline in cognitive development and both functioned in the area of significant developmental delay. The authors postulated that a possible reason for continued deterioration in the twins, despite the demonstration of full chimerism, was a very low level of enzyme throughout the years after transplant. One other patient with MPS III who had received a transplant was 5.3 years old at the time of the transplant, and continued to regress post-transplant.[65]

The few patients with Maroteaux-Lamy and Sly syndrome that have received transplants have shown promising results, with clinical improvement post-transplant.[2]

Other Inherited Metabolic Disorders

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Outcomes with the leukodystrophies and allogeneic HCT have been variable but somewhat promising. In boys and men with X-linked adrenoleukodystrophy; outcomes have depended on disease status at transplant and transplant-related complications[2], but reports of preservation of neuropsychologic and neurologic function have been made.

Nonrandomized Studies

Miller (2011) reported the results of 60 boys who underwent allogeneic HCT for cerebral adrenoleukodystrophy between 2000 and 2009.[66] The median age at HCT was 8.7 years; conditioning regimens and allograft sources varied. At HCT, 50% demonstrated a Loes radiographic severity score of 10 or more, and 62% showed clinical evidence of neurologic dysfunction. A total of 78% (n=47) are alive at a median 3.7 years after HCT. The estimate of five-year survival for boys with Loes score less than 10 at HCT was 89%, whereas that for boys with Loes score of 10 or more was 60% (p=0.03). The five-year survival estimate for boys absent of clinical cerebral disease at HCT was 91%, whereas that for boys with neurologic dysfunction was 66% (p=0.08). The cumulative incidence of transplantation-related mortality at day 100 was 8%. Posttransplantation progression of neurologic dysfunction depended significantly on the pre-HCT Loes score and clinical neurologic status.

Fewer than 40 patients with globoid-cell leukodystrophy have undergone allogeneic HCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function.[2]

Many patients with metachromatic leukodystrophy who have undergone allogeneic HCT and had long-term engraftment have had amelioration of the disease signs and symptoms and prolonged survival.[2]

Mynarek (2011) reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HCT.[67] Patients were diagnosed with the disease at a median age of 2.5 years (range 1.1 to 23 years) and underwent HCT at a median age of 3.6 years (1.3 to 23.1 years). After a median follow-up of 5.5 years (2.1 to 12.6 years), OS was 88%. One patient died 76 days after HCT from sepsis, GVHD and pulmonary hemorrhage and another patient died on day 135 due to viral infections and multi-organ failure. Before HCT, the extent of developmental delay in the 17 patients varied over a wide range. After HCT, patients made developmental progress, however normal development was not achieved. Hearing ability improved in some but not all of the patients.

INFANTILE MALIGNANT OSTEOPETROSIS

The success of allogeneic HCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having a five-year disease-free survival of 73% to 79% versus transplantation with an unrelated or mismatched donor of 13% to 45%.[8]

Nonrandomized Studies

A retrospective analysis of 194 patients with infantile osteopetrosis transplanted between 1990 and 2011 reported five-year disease-free survival of 62% for recipients of HLA-matched sibling transplants, and 42% for recipients of a graft from a matched unrelated donor.[68] Mortality risks were higher after alternative donor compared with HLA-matched sibling donor transplantation (hazard ratio 1.65; 95% CI, 1.04 to 2.62; p=0.03). The most common cause of death was graft

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failure, accounting for 50% of deaths after HLA-matched sibling and 43% of deaths after alternative donor transplantation.

A retrospective analysis of 122 children who received an allogeneic HCT for autosomal recessive osteopetrosis between 1980 and 2001 reported five-year disease-free survival of 73% for recipients of a genotype HLA-identical HCT (n=40), 43% for those of a phenotype HLA-identical or one HLA-antigen mismatch graft from a related donor (n=21), 40% for recipients of a graft from a matched unrelated donor (n=20), and 24% for patients who received an HLA-haplotype-mismatch graft from a related donor (n=41).[69]

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015 the American Society for Blood and Marrow Transplantation published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial settings.[70] Specific to this review, Table 2 provides the allogeneic guidelines for specific indications. Each indication is given a rating, which include:

> (1) Standard of care, where indication for HCT is well defined and supported by evidence, (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but HCT has been shown to be effective therapy, (3) Standard of care, rare indication, for rare diseases where HCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible, (4) Developmental, for diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option, and (5) Not generally recommended, where available evidence does not support the routine use of HCT.

Table 2. Recommendations for Use of Allogeneic HCT to Treat Genetic Diseases and Acquired Anemias

Indications	Allogeneic HCT <18 Years
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S
Fanconi anemia	R
Dyskeratosis congenita	R
Blackfan-Diamond anemia	R
Sickle cell disease	C
Thalassemia	S
Congenital amegakaryocytic thrombocytopenia	R
Severe combined immunodeficiency	R
T-cell immunodeficiency, severe combined immunodeficiency variants	R
Wiskott-Aldrich syndrome	R
Hemophagocytic disorders	R
Lymphoproliferative disorders	R

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Indications	Allogeneic HCT <18 Years
Severe congenital neutropenia	R
Chronic granulomatous disease	R
Other phagocytic cell disorders	R
Immunodysregulation polyendocrinopathy entropathy X-linked syndrome	R
Juvenile rheumatoid arthritis	D
Systemic sclerosis	D
Other autoimmune and immune dysregulation disorders	R
Mucopolysaccharidoses (MPS-I and MPS-VI)	R
Other metabolic diseases	R
Osteopetrosis	R
Globoid cell leukodystrophy (Krabbe)	R
Metachromatic leukodystrophy	R
Cerebral X-linked adrenoleukodystrophy	R
Indication	**Allogeneic HCT >18 Years**
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S
Fanconi anemia	R
Dyskeratosis congenita	R
Sickle cell disease	C
Thalassemia	D
Hemophagocytic syndromes, refractory	R
Mast cell diseases	R
Common variable immunodeficiency	R
Wiskott-Aldrich syndrome	R
Chronic granulomatous disease	R
Multiple sclerosis	N
Systemic sclerosis	N
Rheumatoid arthritis	N
Systemic lupus erythematosus	N
Crohn’s disease	N
Polymyositis-dematomyositis	N

C: clinical evidence available; D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication; S: standard of care.

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SUMMARY

There is enough research to show that allogeneic hematopoietic cell transplantation using myeloablative or reduced-intensity conditioning in select individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome or a genetic disorder affecting skeletal tissue leads to improvement in survival and other disease-specific outcomes. Therefore, allogeneic hematopoietic cell transplantation using myeloablative or reduced-intensity conditioning may be considered medically necessary in select individuals when the policy criteria are met.

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71. BlueCross BlueShield Association Medical Policy Reference Manual "Allogeneic Cell Transplantation for Genetic Diseases and Acquired Anemias." Policy No. 8.01.22

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition

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Codes	Number	Description
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *December 2018*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.26

Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

Effective: November 1, 2019

Next Review: August 2020
Last Review: September 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The use of hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) has been investigated for treatment of patients with epithelial ovarian cancer. Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Note: HCT to treat *germ cell* tumors of the ovary is considered in a separate medical policy (see Cross References).

Autologous and allogeneic hematopoietic cell transplantation are considered **investigational** to treat epithelial ovarian cancer.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

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- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
4. Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).HCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental.

EPITHELIAL OVARIAN CANCER

Several different types of malignancies can arise in the ovary; epithelial carcinoma is the most common. Epithelial ovarian cancer is the fifth most common cause of cancer death in women. New cases and deaths from ovarian cancer in the United States in 2015 are estimated at 21,290 and 14,180, respectively.[1] Most ovarian cancer patients present with widespread disease, and yearly mortality is approximately 65% of the incidence rate.

The current management of advanced epithelial ovarian cancer is cytoreductive surgery followed by combination chemotherapy.[2] Approximately 75% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian cancer, and treated with the combination of paclitaxel and a platinum analog being the preferred

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regimen for newly diagnosed advanced disease.[2,3] The use of platinum and taxanes has improved progression-free survival (PFS) and overall survival (OS) rates in advanced disease to 16–21 months and 32–57 months, respectively.[3] However, most of these women develop recurrences and die of their disease as chemotherapy drug resistance leads to uncontrolled cancer growth.[2]

High-dose chemotherapy (HDC) has been investigated as a way to overcome drug resistance. However, limited data exist on this treatment approach, and the ideal patient population and best regimen remain to be established.[2] Hematopoietic cell transplantation has been studied in a variety of patient groups with ovarian cancer as follows:

- to consolidate remission after initial treatment
- to treat relapse after a durable response to platinum-based chemotherapy
- to treat tumors that relapsed after less than six months
- to treat refractory tumors

EVIDENCE SUMMARY

The principal outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of epithelial ovarian cancer, comparative clinical trials that compare this therapy to standard medical treatment are needed. Further, for treatment of malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

TECHNOLOGY ASSESSMENTS

Initially, this policy was based on a 1998 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment, “High-dose chemotherapy with autologous stem cell support for epithelial ovarian cancer”[4] that reached the following conclusions:

> Data were unavailable from randomized controlled trials for any of the patient groups studied (see Description). Thus, the Assessment was able to compare outcomes only indirectly, using separate studies of high-dose chemotherapy (HDC) and conventional dose regimens.[4] Although some results reported after high-dose therapy appeared encouraging, the indirect comparisons did not permit conclusions.
>
> In previously untreated patients, reported response rates suggested that high-dose therapy increased the objective response rate compared to patients given conventional-dose chemotherapy. However, this comparison was flawed by age bias and by differences in performance status and other baseline characteristics of patients included in the two sets of studies. Response duration and survival data were unavailable for comparison. Treatment-related mortality was greater after high-dose therapy.
>
> In previously treated patients, objective response rates after HDC also were reportedly higher than after conventional-dose regimens. Subgroup analyses showed higher

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response rates among platinum-sensitive, optimally debulked patients. Minimum values of the ranges reported across studies for median response duration and survival after HDC were similar to those reported after conventional-dose chemotherapy. However, the maxima for these ranges suggested improved response duration and overall survival after high-dose therapy. In contrast, data from the Autologous Blood and Marrow Transplant Registry did not show similarly high survival for comparable subgroups. Comparison with conventional-dose chemotherapy was again biased due to differences in age distributions, performance status, and other baseline characteristics of patients included in studies of high-dose or conventional therapies.

The 1998 TEC Assessment did not identify any studies reporting outcomes of allogeneic transplants for patients with ovarian cancer.[4] A separate 1999 TEC Assessment evaluated the use of HDC with allogeneic stem-cell support (HDC/AlloSCS) as salvage therapy after a failed prior course of HDC/AuSCS.[5] There were no data regarding outcomes of this strategy as therapy for epithelial ovarian cancer.

RANDOMIZED CONTROLLED TRIALS

Mobus (2007) reported on a randomized phase III trial that included 149 patients with untreated ovarian cancer who were randomly assigned, after debulking surgery, to standard chemotherapy or sequential HDC and peripheral blood stem-cell support.[3] This was the first randomized trial comparing HDC to standard chemotherapy as first-line treatment of ovarian cancer, and the investigators found no statistically significant difference in progression-free survival (PFS) or overall survival (OS) between the two treatment options. The study was powered such that a sample of 208 patients would be needed to detect an absolute improvement of 15% in PFS with a power of 80% and a one-sided alpha of 5%. The median patient age was 50 years (range: 20–65) and FIGO stage was IIb/IIc in 4%, III in 78%, and IV in 17%. Seventy-six percent of patients in the HDC arm received all of the scheduled chemotherapy cycles. After a median follow-up of 38 months, PFS was 20.5 months in the standard chemotherapy arm and 29.6 months in the HDC arm (hazard ratio [HR]: 0.84; 95% CI: 0.56–1.26; p=0.40). Median OS was 62.8 months in the standard chemotherapy arm and 54.4 months in the HDC arm (HR: 1.17; 95% CI: 0.71–1.94; p=0.54).

Papadimitriou (2008) reported on randomized controlled trial (RCT) the use of HDC with stem-cell support as consolidation therapy in patients with advanced epithelial ovarian cancer (FIGO stage IIC-IV).[2] Patients who achieved first clinical complete remission after conventional chemotherapy were randomly assigned to receive or not receive high-dose melphalan and autologous cell transplant. A total of 80 patients were enrolled in the trial. Of the 37 patients allocated to HDC, 11 did not receive the treatment either due to refusal or failure of peripheral blood stem-cell mobilization. In an intent-to-treat analysis, there were no significant differences between the two arms in time-to-disease progression (p=0.059) or OS (p=0.38).

NONRANDOMIZED STUDIES

Experience with HCT in epithelial ovarian cancer comes primarily from registry data and phase II studies.[6-11] Over the last 20 years, more than 1,000 patients have been entered on transplant registries in Europe and in the United States.[3,6,7] Many of the registry patients were treated in relapse and others in non-randomized studies using HDC as first-line treatment.

Case selection and retrospective review make the interpretation of the registries and non-randomized data difficult.[3] Survival analyses from registry data and clinical trials suggested a

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possible benefit treating ovarian cancer patients with HCT.[3] However, as outlined above, none of the randomized trials have provided evidence that HCT in ovarian cancer provides any outcome benefit.

SUMMARY OF EVIDENCE

For individuals who have advanced-stage epithelial ovarian cancer who receive HCT, the evidence includes randomized trials and data from case series and registries. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment related mortality and morbidity. Although some of the observational studies have reported longer survival in subsets of women with advanced epithelial ovarian cancer than women treated with standard chemotherapy, none of the randomized trial evidence has shown any benefit from HCT in this population. Overall, the evidence has not shown that HCT improves health outcomes in treating epithelial ovarian cancer, including survival, compared with conventional standard doses of chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINE SUMMARY

No current clinical practice guidelines from professional societies address hematopoietic cell transplantation for epithelial ovarian cancer.

SUMMARY

More research is needed to know how well hematopoietic cell transplantation (HCT) works to treat people with epithelial ovarian cancer. In addition, there are no clinical practice guidelines from professional societies that recommend HCT for these patients. Therefore, the use of HCT for the treatment of epithelial ovarian cancer is considered investigational.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)

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	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.27

Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Effective: April 1, 2020

Next Review: January 2021
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

This policy addresses hematopoietic cell transplantation for miscellaneous solid tumors in adults. Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment. Transplantation of cells from both autologous and allogeneic donors for a variety of solid tumors is discussed.

MEDICAL POLICY CRITERIA

Note: This policy addresses only solid tumors in adults. See Cross References section below for tumors not specifically addressed in this policy. See Appendix I for glossary of terms.

Autologous or allogeneic hematopoietic cell transplant is considered **investigational** for all of the following malignancies in adults:

- Bile duct cancer
- Cervical cancer
- Colon cancer

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- Esophageal cancer
- Fallopian tube cancer
- Gall bladder cancer
- Lung cancer, any histology
- Malignant melanoma
- Nasopharyngeal cancer
- Neuroendocrine tumors
- Osteosarcoma
- Pancreas cancer
- Paranasal sinus cancer
- Prostate cancer
- Rectal cancer
- Renal cell cancer
- Soft tissue sarcomas
- Stomach cancer
- Thymus tumors
- Thyroid tumors
- Tumors of unknown primary origin
- Uterine cancer

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

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CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer, Transplant, Policy No. 45.26
4. Hematopoietic Cell Transplantation for Breast Cancer, Transplant, Policy No. 45.29
5. Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33
6. Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas, Transplant, Policy No. 45.34
7. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37
8. Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II gene loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of *allogeneic* HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in

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any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to be delivered at doses that could otherwise not be given without stem cells, which are infused to "rescue" hematopoiesis after high dose therapy. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term "reduced-intensity conditioning" (RIC) will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

HCT IN SOLID TUMORS IN ADULTS

HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors in adults is less well established, although it has been investigated for a variety of solid tumors. With the advent of nonmyeloablative allogeneic transplant, interest has shifted to exploring the generation of alloreactivity to metastatic solid tumors via a graft-versus-tumor effect of donor-derived T cells.[1]

MISCELLANEOUS SOLID TUMORS IN ADULTS

This policy collectively addresses other solid tumors of adults for which HCT has been investigated, including lung cancer; malignant melanoma; tumors of the gastrointestinal tract (including colon, rectum, pancreas, stomach, esophagus, gallbladder, and bile duct tumors); male and female genitourinary systems (e.g., renal cell carcinoma, cervical carcinoma, cancer of the uterus, fallopian tubes, and prostate gland); tumors of the head and neck; soft tissue sarcoma; thyroid tumors; tumors of the thymus; and tumors of unknown primary origin.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and

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Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271.[2] Hematopoietic cells are included in these regulations.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of solid organ malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life may be another primary outcome, particularly among patients living with refractory disease. In order to understand the impact of hematopoietic cell transplantation for treatment of solid tumors in adults on these outcomes, systematic reviews (SRs) of well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as conventional standard-dose chemotherapy are needed. In indications for which RCTs are not available, non-controlled studies are considered. Further, for treatment of malignant cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION IN SOLID TUMORS OF ADULTS

A review published by Pedrazzoli (2007) concluded broadly that “data available to date do not support the routine use of HDC [high-dose chemotherapy] with AHSCT [autologous HCT] for solid tumors other than [breast cancer] in adults.”[3] Pedrazzoli also published results from a previous review of AHSCT for solid tumors in adults in 2006, concluding that insufficient evidence exists to support its use in small cell lung cancer and soft tissue sarcoma.[4] Finally, another review published in 1999 by Nieto concluded that evidence was inadequate to demonstrate a survival benefit from HDC and AHCT for melanoma or soft tissue sarcoma.[5] Overall, the literature is insufficient and does not permit conclusions about the use of this therapy in adults with solid tumors.

Urothelial Carcinoma

Limited data exist on the use of autologous HCT for urothelial carcinoma. To date, only a single uncontrolled pilot study on HDC with HCT for patients with refractory urothelial carcinoma has been published by Nishimura (1999).[6] This study was unable to provide evidence of improved outcomes.

Nasopharyngeal Carcinoma

A single uncontrolled pilot study by Airoldi (2001) on HDC with autologous HCT for patients with recurrent or advanced nasopharyngeal carcinoma fails to provide evidence to support the use of this treatment for this indication.[7]

Adult Soft Tissue Sarcomas

<u>Systematic Reviews</u>

In 2014, a Cochrane SR evaluated the use of autologous HCT following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas.[8] The authors included 62

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studies reporting on 294 transplanted patients with a variety of soft tissue sarcomas. One randomized controlled trial (RCT) with 83 patients was identified[9]; the remaining studies were single-arm studies. In the RCT, OS was not statistically significantly different between autologous HCT following high-dose chemotherapy compared with standard-dose chemotherapy (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.70 to 2.29; p=0.44), and the point estimate for survival at three years was 32.7% compared with 49.4%. The pooled treatment-related mortality rate across the single-arm studies was 15/294 (5.1%). The authors concluded that the available evidence from small phase II studies was insufficient to support the use of autologous HCT in adult patients with soft tissue sarcoma.

Another systematic review, published in 2008 by Verma, found three phase III RCTs involving HCT, none of which evaluated the therapy for first-line treatment of advanced or metastatic adult soft tissue sarcoma compared to conventional standard-dose chemotherapy.[10]

Hartmann (2013) published results of a phase II study of high-dose chemotherapy with ifosfamide, carboplatin, and etoposide (HD-ICE) followed by peripheral blood stem cell transplantation in patients with grade 2 or 3 histologically-proven soft tissue sarcoma that were considered unresectable or marginally resectable.[11] Thirty patients were enrolled, 14 of whom did not receive all allocated interventions due to progressive disease (n=5), ifosfamide-related neurotoxicity (n=6), withdrawal of consent (n=1), complete remission (n=1), and insufficient stem-cell harvest (n=1). Eighteen patients underwent radiation: five preoperatively, 12 postoperatively, and with palliative intent in one. Twenty-four of 30 (80%) patients underwent surgery with macroscopically complete tumor resection. In the subgroup of patients who underwent consolidation high-dose chemotherapy, surgery revealed R0-margins (microscopically margin-negative resection) in 12 patients (75%), while four patients had R1-margins (macroscopically margin-negative but microscopically margin-positive resection). In the subgroup of patients treated without HD-ICE consolidation, seven of the eight patients had R1-margins. Severe hematologic toxicity occurred in most patients, and eight patients developed febrile neutropenia. One patient developed myelodysplastic syndrome after 25 months of follow-up. After a median follow-up period of 50 months (range, 26–120 months) in surviving patients, the median PFS of all patients was 21 months (range, 1–94) and median OS was 37 months (range, 3–120 months), corresponding to five-year PFS and OS rates of 39% and 48%, respectively. The authors conclude that induction chemo-/ radiotherapy and the role of dose intensification should be further studied until potential alternatives of targeted therapies become available for further distinct subtypes of adult type sarcomas.

Kasper (2010) reported the results of a prospective, single institution phase II trial that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma.[12] After four courses of chemotherapy, patients with at least a partial response underwent high-dose chemotherapy and autologous HCT (n=9). All other patients continued chemotherapy for two more cycles. Patients treated with HCT had statistically significant longer PFS and OS compared with patients treated with standard chemotherapy, although only nine of 34 patients were selected for treatment with HCT.

Schlemmer published a phase II study in 2006 on 55 patients with metastatic soft tissue sarcoma.[13] Although significantly more patients receiving autologous HCT responded to doxorubicin-based induction chemotherapy versus the control group (14% vs. 3%; p=0.003), the estimated OS was not statistically different between those that received autologous HCT and those that did not.

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In 2007, Kasper published results of a cases series of 21 patients with soft-tissue sarcoma, which showed a PFS and an OS benefit only in patients with no evidence of disease before receiving HDC and autologous HCT.[14]

Small-Cell Lung Carcinoma

In 2009, Jiang published results from a systematic review and meta-analysis of the medical literature through October 2008, including English language studies using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC.[15] The meta-analysis consisted of five RCTs (three were phase III trials and two were phase II), for a total of 641 patients. They found no significant increase in the likelihood of an improved response rate with autologous transplant versus control chemotherapy. Neither did they find a statistically significant increase in OS among the autologous transplant patients compared to control regimens. The authors concluded that current evidence does not support the use of intensified chemotherapy and autologous HCT for treating SMLC.

One smaller randomized study and several single-arm studies of HDC and autologous HCT for SCLC are summarized in a 2007 systematic review article by Crivellari.[16] The authors begin the conclusion of their review with this statement, “The lesson we have learned is that the current literature indicates that there is no evidence that the treatment of SCLC can be improved by increasing the dose intensity, peak dose, or total dose of chemotherapy, and survival rates have reached a plateau, so intensification strategy should probably be abandoned.”

In 2005, Lorigan reported on a randomized phase III trial of 318 patients with SCLC to investigate whether doubling the dose density of ifosfamide, carboplatin, and etoposide (ICE) chemotherapy with filgrastim and blood-progenitor-cell support (dose-dense arm) improves survival, compared with standard ICE chemotherapy (standard arm).[17] No statistically significant difference in response rates was seen between the two groups (80% response rate in the standard arm vs. 88% in the dose-dense arm), nor was there a statistically significant difference in OS between the two groups. Statistically significantly more hematologic toxicity was reported in the dose-dense arm than in the standard arm, but the number of cycles complicated by neutropenic sepsis was statistically significantly higher in the standard arm than in the dose-dense arm (15.3% versus 11.6%, respectively; difference = 3.7%, 95% CI = −4.1% to 11.5%; p = .03).

Autologous Hematopoietic Cell Transplantation in Solid Tumors of Adults Section Summary

For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes two SRs reporting one RCT, as well as three phase 2 single-arm studies, and a case series. Although small phase 2 studies reported either increased response to treatment or longer survival for patients treated with HCT than with standard chemotherapy, the available RCT did not show a survival benefit with autologous HCT. For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes two SRs and one randomized study. Overall, the majority of the data from these studies, including the randomized study, showed no increased OS with autologous HCT. At least one systematic review on this topic recommended that autologous HCT as a dose intensification strategy for SCLC be abandoned in light of evidence demonstrating no clear treatment benefit.[16] Evidence for the use of autologous HCT in other solid tumors in adults, including urothelial carcinoma

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and nasopharyngeal carcinoma is limited and consists of small, uncontrolled studies that fail to demonstrate improved health outcomes with the use of autologous HCT in the treatment of these tumor types.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN SOLID TUMORS OF ADULTS

Multiple Indications

A 2008 review of data from the European Bone Marrow Transplantation Solid Tumors Working Party (EBMT STWP) on allogeneic HCT for renal cell cancer, pancreatic cancer, colorectal cancer and soft-tissue sarcoma found multiple small case series (n≤25) with different conditioning regimens, varying response rates and treatment mortality rates for each indication.[18] The EBMT STWP concluded that, “Allogeneic transplantation in renal cancer and other solid tumors should be considered a developmental therapy until definitive proof of a clinical benefit is achieved by current studies.”

Mixed Tumor Types

In 2016, Omazic reported on a long-term follow-up on 61 patients with a variety of solid tumor types considered to be incurable with any conventional therapy who were treated with allogeneic HCT from 1999 to 2012.[19] Tumors included metastatic renal carcinoma (n=22), cholangiocarcinoma (n=17), colon cancer (n=15), prostate cancer (n=3), pancreatic adenocarcinoma (n=3), and breast cancer (n=1). Most patients (n=59) had undergone surgical debulking of the primary tumor, and 31 patients had previously undergone additional therapy with cytotoxic chemotherapy, radiotherapy, or immunotherapy. Conditioning was myeloablative in 23 patients, reduced in 36 patients, and nonmyeloablative in two patients. Over a median follow-up of eight years, the rate of OS at five and ten years were 15% and 9%, respectively.

Nasopharyngeal Carcinoma

In 2011, Toh reported the outcomes of a phase II trial of 21 patients with pretreated metastatic nasopharyngeal carcinoma.[20] Previous treatment was not uniform; patients had received a median of two previous chemotherapy regimens (range 1-8). All patients had extensive metastases. Patients underwent nonmyeloablative allogeneic HCT with sibling allograft. Seven patients (33%) showed a partial response and three (14%) achieved stable disease. Four patients were alive at two years and three showed prolonged disease control past 344 days. One and two-year OS rates were 29 and 19%, respectively, comparable to the median 7-14 months OS reported in the literature for metastatic nasopharyngeal patients treated with salvage chemotherapy without HCT. However, valid and reliable conclusions based upon these results cannot be made due to limitations such as: small sample size, varied pre-HCT treatment regimens, and lack of control group. These limitations hinder the ability to account for the many types of bias that can affect study outcomes.

Renal Cell Carcinoma

Metastatic renal cell carcinoma (RCC) has an extremely poor prognosis, with a median survival of less than one year and a five-year survival of less than 5%.[21] RCC is relatively resistant to chemotherapy, but is susceptible to immune therapy. Interleukin-2 (IL-2) and/or interferon alpha have induced responses and long-term PFS in 4%–15% of patients.[18] In addition, seven targeted therapies have the U.S. Food and Drug (FDA) approval for treatment

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of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizuman.[22] Based on the susceptibility of RCC to immune therapies, the immune-based strategy of a graft-versus-tumor effect possible with an allogeneic transplant has led to an interest in its use in RCC. Several small case series and pilot studies exist on the use of allogeneic HCT in RCC.

In 2009, Bregni assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received a reduced intensity conditioning (RIC) allograft from a sibling who was human leukocyte antigen (HLA) identical.[23] All patients received the same conditioning regimens. Response to allograft was available in 24 patients, with a complete response in one patient and partial response in four patients. Twelve patients had minor response or stable disease, and seven reported progressive disease. Overall response rate (complete plus partial) was 20%. Six patients died because of transplant-related complications. Median survival was 336 days (12–2,332+). One-year OS was 48% (95% CI: 28–68), and five-year OS was 20% (95% CI: 4–36). The authors concluded that allografting may be associated with long-term disease control in only a small fraction of cytokine-resistant patients with RCC.

In 2000, Childs published a study on the first series of patients with RCC treated with nonmyeloablative allogeneic HCT.[21] The investigators showed regression of the tumor in ten of 19 (53%) patients with cytokine-refractory, metastatic RCC who received an HLA-identical sibling allogeneic HCT. Three patients had a complete response, and remained in remission 16, 25, and 27 months after transplant. Four of seven patients with a partial response were alive without disease progression nine to19 months after transplantation. Other pilot trials have demonstrated the graft-versus-tumor effect of allogeneic transplant in metastatic RCC, but most have not shown as high a response rate as the Childs' study.[24] Overall response rates in these pilot trials have been about 25%, with complete response rates of about 8%.

Colorectal Cancer

In 2009, Aglietta reported their experience with 39 patients with metastatic colorectal cancer who underwent RIC allogeneic HCT between 1999 and 2004 at nine European Group for Blood and Marrow Transplantation (EBMT) centers.[25] Patients were treated with one of five different RIC regimens. Patient population characteristics were heterogeneous; pretransplant disease status was partial response in two patients, stable disease in six patients, and progressive disease in 31. After transplant, tumor responses were complete in 2% of patients, partial in 18%, and 26% of patients had stable disease, for overall disease control in 46% of patients. Transplant-related mortality was 10%. Median overall follow-up was 202 days (range, 6–1,020), after which time 33 patients had died. Tumor progression was the cause of death in 74% of patients. Achievement of response after transplantation was associated with a difference in OS, with the 18 patients who had a response having a median OS of approximately 400 days versus approximately 120 days for those who had no response (p=.00018). The authors concluded that the HCT approach should probably be reserved for patients with a partial response or stable disease after second-line therapy for metastatic colorectal cancer, and that second-generation clinical trials in these patients are warranted.

Pancreatic Cancer

In 2009, Abe reported the outcomes for five patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative allogeneic peripheral blood HCT.[26] The median patient age was 54 years (range: 44–62 years). All patients had advanced disease, either with metastases or peritonitis, and had received at

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least one course of chemotherapy including gemcitabine. After HSCT, tumor response was only observed in two patients; one patient had complete disappearance of the primary tumor and one had a 20% reduction in tumor size. Four patients died of progressive disease on post-transplant day ranging from 28 to day 209 (median: 96 days).

In 2008, Kanda reported on the efficacy of RIC allogeneic HCT against advanced pancreatic cancer in 22 patients from three transplantation centers in Japan.[27] The RIC regimens differed among the centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and seven having locally advanced disease. All but one patient received chemotherapy of various combinations before transplant, and ten patients received local radiation. After HCT, one patient achieved complete response, two patients had partial response, two had minor response, and eight had stable disease, with an overall response rate of 23%. Median survival was 139 days, and the major cause of death was tumor progression (median duration of survival in advanced pancreatic cancer in the nontransplant setting is less than six months, even in patients treated with gemcitabine). Only one patient survived longer than one-year after transplantation. The authors concluded that a tumor response was observed in one-fourth of patients with advanced pancreatic cancer who underwent HCT and that the response was not durable.

Allogeneic Hematopoietic Cell Transplantation in Solid Tumors of Adults Section Summary

For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allogeneic HCT, the evidence includes uncontrolled, small, single-arm studies. These studies are limited by small sample size, varied pre-HCT treatment regimens, and lack of control groups.

EVIDENCE SECTION SUMMARY

Principal outcomes associated with the treatment of solid organ malignancies are overall survival, disease-specific survival, and treatment related mortality and morbidity. There is not enough evidence that hematopoietic cell transplant (HCT) in the treatment of miscellaneous solid tumors in adults improves overall survival, disease-specific survival, or treatment-related mortality or morbidity. Further research is needed to determine whether there is an association between HCT and these outcomes, and if this association is uniform across all patient populations.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The most recent National Comprehensive Cancer Network (NCCN) guidelines on the tumors addressed in this policy do not discuss hematopoietic cell transplantation as a treatment option.[22,28-31]

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) issued guidelines related to indications for autologous and allogeneic hematopoietic cell transplantation.[32] The tumors addressed in this review for which ASBMT provides recommendations are as follows:

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- Ewing's sarcoma, high risk: allogeneic HCT – N ("not generally recommended"); autologous HCT – C ("standard of care, clinical evidence available")
- Renal cancer, metastatic: allogeneic HCT – D ("developmental"); autologous HCT – N ("not generally recommended").

SUMMARY

There is not enough research to show that hematopoietic cell transplantation (HCT) improves health outcomes for adult patients with the tumors addressed in this policy. Therefore, HCT is considered investigational for these indications.

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33. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Stem-Cell Transplant for Miscellaneous Solid Tumors in Adults." Policy No. 8.01.24

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic

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Codes	Number	Description
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.28

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Effective: April 1, 2020

Next Review: January 2021
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic hematopoietic cell transplant (HCT) using a myeloablative conditioning regimen may be considered **medically necessary** to treat any one of the following:
   1. Poor- to intermediate-risk AML in first complete remission (CR1) (i.e., abnormal cytogenetics; see Policy Guidelines for information on risk stratification)
   2. Primary refractory AML for which intensified induction chemotherapy is planned to achieve complete remission (i.e., leukemia that does not achieve a complete remission after conventional-dose chemotherapy)
   3. Relapsed AML for which intensified induction chemotherapy is planned to achieve second complete remission (CR2) or beyond
   4. Relapsed AML following prior autologous HCT in patients who are medically able to tolerate intensified induction chemotherapy, and for whom that chemotherapy is planned to achieve complete remission

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II. Allogeneic HCT using a reduced-intensity conditioning regimen may be considered **medically necessary** as a treatment of AML in patients who are in complete marrow and extramedullary remission (CR1 and beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen (see Policy Guidelines).

III. Autologous HCT may be considered **medically necessary** to treat AML for any indication other than as first line treatment (e.g., first or second remission or relapsed AML if responsive to intensified induction chemotherapy).

IV. Hematopoietic cell transplantation is considered **investigational** to treat AML for any other circumstance other than those listed above, including but not limited to an autologous HCT as first line treatment.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

RISK STRATIFICATION

The National Comprehensive Cancer Network (NCCN) preferred risk stratification for AML is based on large datasets from consortia group, multi-center trials. NCCN algorithms for individual patient prognosis and management guidance are based on the following table:[1]

European LeukemiaNET Risk Stratification by Genetics in Non-APL

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;22.1); *RUNX1-RUNX1T1* inv(16)(p13.q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD Wild-type *NPM1* without *FLT3*-ITD or with *FLT3-ITD* (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p)

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Risk Category	Genetic Abnormality
	Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3-ITD* Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Autologous HCT is used for consolidation treatment of intermediate- to poor-risk disease in complete remission, among patients for whom a suitable donor is not available. Favorable-risk AML often responds well to chemotherapy with prolonged remission if not cure.

REDUCED INTENSITY CONDITIONING

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HCT. These include those whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient whose disease relapses following a conventional myeloablative allogeneic HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HCT if a complete remission could be re-induced with chemotherapy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

CROSS REFERENCES

1. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
2. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
3. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
4. Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Transplant, Policy No. 45.24

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives

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HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called “graft versus tumor” effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II gene loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional (“classical”) practice of *allogeneic* HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to be delivered at doses that could otherwise not be given without stem cells, which are infused to “rescue” hematopoiesis after high dose therapy. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell

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engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term “reduced-intensity conditioning” (RIC) will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) (sometimes called “acute nonlymphocytic leukemia” [ANLL]) refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. AML is characterized by proliferation of myeloblasts, coupled with low production of mature red blood cells, platelets, and often non-lymphocytic white blood cells (granulocytes, monocytes). Clinical signs and symptoms are associated with neutropenia, thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. About 13,000 new cases are diagnosed annually.

The pathogenesis of AML is unclear. It can be subdivided according to resemblance to different subtypes of normal myeloid precursors using the French-American-British (FAB) classification. This system classifies leukemias from M0–M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization (WHO) subsequently incorporated clinical, immunophenotypic and a wide variety of cytogenetic abnormalities that occur in 50% to 60% of AML cases into a classification system that can be used to guide treatment according to prognostic risk categories (see Policy Guidelines). In 2016, the WHO system updated subcategories of AML including: 1) AML with recurrent genetic abnormalities; 2) AML with myelodysplasia-related changes; 3) therapy-related AML myeloid neoplasms; 4) AML not otherwise specified (NOS); 5) myeloid sarcoma; and 5) myeloid proliferations related to Down syndrome.

Molecular studies have identified a number of genetic abnormalities that also can be used to guide prognosis and management of AML. Cytogenetically normal AML (CN-AML) is the largest defined subgroup of AML, comprising about 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic mutations that affect outcomes, of which six have been identified. The *FLT3* gene that encodes FMS-like receptor tyrosine kinase (TK) 3, a growth factor active in hematopoiesis, is mutated in 33%–49% of CN-AML cases; among those, 28%–33% consist of internal tandem duplications (ITD), 5%–14% are missense mutations in exon 20 of the TK activation loop, and the rest are point mutations in the juxtamembrane domain. All *FLT3* mutations result in a constitutively activated protein, and confer a poor prognosis. Several pharmaceutical agents that inhibit the *FLT3* TK are under investigation.

Complete remissions can be achieved initially using combination chemotherapy in up to 80% of AML patients. However, the high incidence of relapse has prompted research into a variety of post-remission strategies using either allogeneic or autologous HCT.

EVIDENCE SUMMARY

Hematopoietic cell transplantation (HCT) has been investigated as consolidation therapy for patients whose disease enters complete remission following initial induction treatment, or as

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salvage therapy in patients who experience disease relapse or have disease that is refractory to induction chemotherapy.

CONSOLIDATION THERAPY IN REMISSION

Allogeneic HCT

In order to understand the impact of allogeneic HCT as consolidation therapy in remission, well-designed randomized controlled trials (RCTs) are preferred. However, these are often difficult to perform given the populations involved. Therefore, this evidence section includes meta-analyses of nonrandomized studies and larger nonrandomized studies in addition to RCTs.

A 2015 meta-analysis examined prospective trials of adult patients with intermediate risk AML in first complete remission (CR1) who underwent either allogeneic or autologous HSCT.[2] The analysis included nine prospective, controlled studies that enrolled a total of 1950 patients between the years 1987 and 2011, with study sizes ranging from 32 patients to 713. Allogeneic HSCT was associated with significantly better relapse-free survival (RFS), overall survival (OS), and relapse rate (RR) than autologous HSCT and/or chemotherapy (hazard ratio [HR],0.684; 95% confidence interval [CI], 0.48 to 0.95; HR=0.76; 95% CI 0.61 to 0.95; HR=0.58; 95% CI 0.45 to 0.75, respectively). Treatment related mortality (TRM) was significantly higher following allogeneic HSCT than autologous HSCT (HR=3.09; 95% CI 1.38 to 6.92). However, a subgroup analysis showed no OS benefit for allogeneic HSCT over autologous HSCT (HR=0.99; 95% CI 0.70 to 1.39).

A meta-analysis of allogeneic HSCT in patients with AML in first complete remission (CR1) pooled data from five studies that included a total of 3,100 patients.[3] Among those patients, 1,151 received allogeneic HSCT, and 1,949 were given alternative therapies including chemotherapy and autologous HSCT. All of the studies employed natural randomization based on donor availability, and an intention-to-treat analysis, with overall survival (OS) and disease-free survival (DFS) as outcomes of interest. This analysis showed a significant advantage of allogeneic HSCT in terms of OS for the entire cohort (fixed-effects model HR=1.17 95% CI 1.06 to 1.30; p=0.003; random-effects model HR=1.15, 95% CI 1.01 to 1.32; p=0.037) even though none of the individual studies did so. Meta-regression analysis showed that the effect of allogeneic HSCT on OS differed depending on the cytogenetic risk groups of patients, suggesting significant benefit for poor-risk patients (HR=1.39, 95% CI not reported), indeterminate benefit for intermediate-risk cases, and no benefit in better-risk patients compared to alternative approaches. The authors caution that the compiled studies used different definitions of risk categories (e.g., SWOG, MRC, EORTC/GIMEMA), but examination shows cytogenetic categories in those definitions are very similar to the recent guidelines from the NCCN outlined in the Policy Guidelines.[4] Furthermore, the statistical power of the meta-regression analysis is limited by small numbers of cases. However, the results of this meta-analysis are supported in general by data compiled in other reviews.[5-8] Together, the body of evidence in the context of clinical review of this policy clearly supports the conclusion that myeloablative allogeneic HSCT may be considered medically necessary for patients with poor- to intermediate-risk AML in CR1. Because better-risk AML typically responds well to conventional induction chemotherapy, allogeneic HSCT may be reserved for treatment of relapsed disease in these patients.

Evidence from the meta-analysis cited here suggests patients with cytogenetically defined better-prognosis disease may not realize a significant survival benefit with allogeneic HSCT in

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CR1 that outweighs the risk of associated morbidity and non-relapse mortality (NRM). However, there is considerable genotypic heterogeneity within the three World Health Organization (WHO) cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics.[9] For example, patients with better-prognosis disease (for example, core-binding factor AML) based on cytogenetics, and a mutation in the *c-Kit* gene of leukemic blast cells, do just as poorly with postremission standard chemotherapy as patients with cytogenetically poor-risk AML.[10] Similarly, individuals with cytogenetically normal AML (intermediate-prognosis disease) can be subcategorized into groups with better or worse prognosis based on the mutational status of the nucleophosmin gene (*NPM1*) and the *FLT3* gene (defined above in the Policy Description). Thus, patients with mutations in *NPM1* but without *FLT3*-ITD have postremission outcomes with standard chemotherapy that are similar to those with better-prognosis cytogenetics; in contrast, patients with any other combination of mutations in those genes have outcomes similar to those with poor-prognosis cytogenetics.[11] These examples highlight the rapidly growing body of evidence for genetic mutations as additional predictors of prognosis and differential disease response to different treatments. It follows that because the earlier clinical trials compiled in the meta-analysis described here did not account for genotypic differences that affect prognosis and alter outcomes, it is difficult to use the primary trial results to draw conclusions concerning the role of allogeneic HCT in different patient risk groups.

A second meta-analysis incorporated data from 24 trials involving a total of 6,007 patients who underwent allogeneic HSCT in first complete remission [CR1].[12] Among the total, 3,638 patients were stratified and analyzed according to cytogenetic risk (547 good-, 2,499 intermediate-, 592 poor-risk AML, respectively) using a fixed-effects model. Compared with either autologous HSCT or additional consolidation chemotherapy, the HR for OS among poor-risk patients across 14 trials was 0.73 (95% CI 0.59 to 0.90; p<0.01); among intermediate-risk patients across 14 trials, the HR for OS was 0.83 (95% CI 0.74 to 0.93; p<0.01); among good-risk patients across 16 trials, the HR for OS was 1.07 (95% CI 0.83 to 1.38; p=0.59). Inter-study heterogeneity was not significant in any of these analyses. Results for DFS were very similar to those for OS in this analysis. These results concur with those from the previously cited meta-analysis and the current Policy Statements for use of allogeneic HCT as consolidation therapy for AML.

A 2014 study by Stelljes compared the outcome of 185 matched pairs of patients from a large multicenter clinical trial (AMLCG99).[13] Patients younger than 60 years who underwent allogeneic HSCT in CR1 were matched to patients who received conventional postremission chemotherapy. The main matching criteria were AML type, cytogenetic risk group, patient age, and time inCR1. In the overall pairwise-compared AML population, the projected seven-year OS rate was 58% for the allogeneic HSCT and 46% for the conventional postremission treatment group (p=037; log-rank test). Relapse-free survival was 52% in the allogeneic HSCT group compared with 33% in the control group (p<0.001). OS was significantly better for allogeneic HSCT in patient subgroups with nonfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome. For the entire patient cohort, postremission therapy was an independent factor for OS (HR=0.66; 95% CI, 0.49 to 0.89 for allogeneic HSCT versus conventional chemotherapy), among age, cytogenetics, and bone marrow blasts after the first induction cycle.

In 2017, Heidrich conducted retrospective analyses of subgroups from two prospective clinical trials, including 497 patients with intermediate-risk AML who did not present with *NPM1*, *CEBPA*, or *FLT3* internal tandem duplication (ITD) variants.[14] During the initial analysis (donor

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vs no-donor), RFS rates were better for patients who had an available sibling donor (n=83) than for those who lacked a matched sibling donor (49% vs 26%; HR=0.5; 95% CI, 0.3 to 0.9; p=0.02); a similar improvement was seen for OS, although not statistically significant (p=0.08). The authors also conducted a time-dependent multivariate analysis to account for the significantly longer time-from-CR1 observed in patients treated with allo-HCT (median, 115 days) compared with those treated with postremission chemotherapy (median, 78 days; p<0.001). Rates of OS after five years were superior for the group who received allo-HCT than for those receiving chemotherapy (OS, 66% vs 46%, respectively; HR=0.58; 95% CI 0.37 to 0.9; p=0.02), as were rates of RFS (five-year RFS, 55% vs 31%; HR=0.51; 95% CI 0.34 to 0.76; p=0.001). The investigators acknowledged that 38% of the group assigned to post-remission chemotherapy received allo-HCT following a relapse, which might have contributed to a crossover effect.

In 2017, Canaani published a retrospective analysis of 1275 patients who underwent HCT; of these, 918 patients had normal white blood cell (WBC) counts, and the rest presented with abnormally high WBC (hyperleukocytosis).[15] For 159 patients in the latter group, WBC counts were between 50,000 and 100,000/µL; for 198 patients, WBC counts were greater than 100,000. By comparing endpoints such as relapse incidence, leukemia-free survival, nonrelapse mortality, and the occurrence of acute or chronic graft-versus-host disease (GVHD) between groups, the authors evaluated hyperleukocytosis as a potential prognostic indicator of outcomes following transplantation. At baseline, patients in the intermediate- and high-WBC groups had younger median ages (49.1 years and 48.8 years, respectively) than patients without hyperleukocytosis (median age, 52.2 years); additionally, patients with high WBC were associated with the presence of FLT3-ITD and NPM1 variants (p<0.001), and there were significant differences between groups regarding cytogenetic risk category (p<0.001) and the choice of conditioning regimen, whether myeloablative or reduced-intensity (p=0.02). In multivariate analysis, patients with hyperleukocytoses (intermediate and high WBC) were more likely to experience relapse than patients with less than 50,000/µL WBC (29% and 30% vs 22%, respectively); the HR was 1.55 (95% CI 1.14 to 2.12; p=0.004). Negative outcomes were again linked to patients with hyperleukocytosis for leukemia-free survival and OS, which were favorable for non-hyperleukocytosis patients (respective HRs were as follows: 1.38 [95% CI 1.07 to 1.78], p=0.013; and 1.4 [95% CI 1.07 to 1.87], p=0.013). Such findings were statistically significant when different types of transplantation sources (a matched sibling vs an unrelated donor) were accounted for, leading investigators to recommend the use of hyperleukocytosis as a predictor of clinical outcomes following allogeneic HCT.

Autologous HCT

A meta-analysis examined survival outcomes of autologous HSCT in CR1 versus standard chemotherapy or no further treatment in AML patients aged 15-55 years.[16] Two types of studies were eligible: 1) prospective cohort studies in which patients with an available sibling donor were offered allogeneic HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and 2) randomized trials that compared autologous HSCT with chemotherapy in all patients. Among a total of 4,058 patients included in six studies, 2,989 (74%) achieved CR1; 1,044 (26%) were randomly allocated to HSCT (n=524) or chemotherapy (n=520). Of the five studies for which OS data were available, outcomes with autologous HSCT were better in three, and outcomes with chemotherapy were better in two. None of the differences reached statistical significance, nor did the pooled estimate reach statistical significance (fixed-effects model survival probability ratio=1.01; 95% CI 0.89 to 1.15, p=0.86). In all six studies, disease-free survival (DFS) was

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numerically superior with autologous HSCT compared to chemotherapy (or no further treatment), but only one reported a statistically significant DFS probability associated with autologous HSCT. However, the pooled estimate for DFS showed a statistically significant probability in favor of autologous HSCT at 48 months post-transplant (fixed-effects model survival probability ratio=1.24, 95% CI 1.06 to 1.44, p=0.006).

There are several possible reasons this meta-analysis did not demonstrate a statistically significant OS advantage for autologous HSCT compared to chemotherapy given the significant estimate for DFS benefit. First, the pooled data showed a 6.45% greater NRM rate in autologous HSCT recipients compared to chemotherapy recipients. Second, 14% of chemotherapy recipients whose disease relapsed ultimately achieved a sustained second remission after undergoing an allogeneic or autologous HSCT. The intent-to-treat analysis in the studies, which included the latter cases in the chemotherapy group, may have inappropriately inflated overall survival rates favoring chemotherapy. Furthermore, this analysis did not take into account potential effects of cytogenetic or molecular genetic differences among patients that are known to affect response to treatment. Finally, the dataset comprised studies performed between 1984 and 1995, during which transplant protocols and patient management evolved significantly, particularly compared to current care. Nonetheless, the evidence suggests the use of autologous HCT to treat AML in CR1 is feasible and offers improved survival and a chance for cure compared to postremission chemotherapy in patients who lack a suitable stem-cell donor.

A second meta-analysis published in 2010 evaluated autologous HSCT versus further chemotherapy or no further treatment for AML in CR1.[17] A total of 9 randomized trials involving 1,104 adults who underwent autologous HSCT and 1,118 who received additional chemotherapy or no additional treatment were identified. The analyses suggest that autologous HSCT in CR1 was associated with statistically significant reduction of relapse risk (RR = 0.56, 95% CI 0.44 to 0.71, p = 0.0004) and significant improvement in DFS (HR = 0.89, 95% CI 0.80 to 0.98), but at the cost of significantly increased NRM (RR = 1.90, 95% CI 0.72 to 0.87, p=0.0002). There were more deaths during the first remission among patients assigned to autologous HSCT than among the chemotherapy recipients or further untreated patients. As a consequence of increased NRM, no statistical difference in OS (HR = 1.05, 95% CI 0.91 to 1.21) was associated with the use of autologous HSCT compared to further chemotherapy or no further therapy. These results were concordant with those of the earlier meta-analysis cited above.

A prospective, randomized phase III trial compared autologous HSCT with intensive consolidation chemotherapy among patients (16-60 years old) with newly diagnosed AML of similar risk profiles in complete remission (CR1).[18] Patients in CR1 after two cycles of intensive chemotherapy (etoposide and mitoxantrone), who were not candidates for allogeneic HSCT, were randomly allocated between a third consolidation cycle of the same chemotherapy (n = 259) or autologous HSCT (n=258). The HSCT group showed a trend toward superior relapse-free survival, the primary outcome, compared to chemotherapy recipients (38% vs. 29%, respectively at five years, p=0.065, 95% CI 0.66 to 1.1). HSCT patients had a lower relapse rate at 5 years compared to chemotherapy recipients (58% vs. 70%, respectively, p=0.02). Overall survival did not differ between HSCT and chemotherapy recipients, respectively (44% vs. 41%, p=0.86). NRM was more frequent in the autologous HSCT group than in the chemotherapy consolidation group (4% vs. 1%, respectively, p=0.02). Despite this difference in NRM, the relative equality of OS rates was attributed by the investigators to a higher proportion of successful salvage treatments – second-line

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chemotherapy, autologous or allogeneic HSCT - in the chemotherapy consolidation recipients that were not available to the autologous HSCT patients. This large study shows an advantage for post-remission autologous HSCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy consolidated patients.

PRIMARY REFRACTORY AML

Conventional-dose induction chemotherapy will not produce remission in 20% to 40% of patients with AML, connoting refractory AML.[4] An allogeneic HCT using a matched related donor (MRD) or matched unrelated donor (MUD) represents the only potentially curative option for these individuals. In several retrospective studies OS rates have ranged from 13% at five years to 39% at three years, although this procedure is accompanied by NRM rates of 25% to 62% in this setting.[5,19] For patients who lack a suitable donor (MRD or MUD), alternative treatments include salvage chemotherapy with high-dose cytarabine or etoposide-based regimens, monoclonal antibodies (e.g., gemtuzumab ozogamicin), multidrug resistance modulators, and other investigational agents such as *FLT3* antagonists.[20] Because it is likely that stem-cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, autologous HCT has no role in patients who fail induction therapy.

RELAPSED AML

Most patients with AML will experience disease relapse after attaining a first complete remission.[4] Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved. Retrospective data compiled from 667 of 1,540 patients entered in three phase III trials suggest allogeneic HSCT in CR2 can produce five-year OS rates of 26% to 88%, depending on cytogenetic risk stratification.[21] Because reinduction chemotherapy treatment may be associated with substantial morbidity and mortality, patients whose disease has relapsed and who have a suitable donor may proceed directly to allogeneic HCT.

In patients without an allogeneic donor, or those who are not candidates for allogeneic HSCT due to age or other factors, autologous HSCT may achieve prolonged DFS in 9% to 55% of patients in CR2 depending on risk category.[22,23] However, because it is likely that stem-cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, and it is often difficult to achieve CR2 in these patients, autologous HSCT in this setting is usually limited to individuals who have a sufficient stem-cell preparation remaining from collection in CR1.[22]

Allogeneic HSCT is often performed as salvage for patients who have relapsed after conventional chemotherapy or autologous HSCT.[22] The decision to attempt reinduction or proceed directly to allogeneic HSCT is based on the availability of a suitable stem-cell donor and the likelihood of achieving a remission, the latter being a function of cytogenetic risk group, duration of CR1, and the patient’s health status. Registry data show DFS rates of 44% using sibling allografts and 30% with MUD allografts at five years for patients transplanted in CR2, and DFS of 35%–40% using sibling transplants and 10% with MUD transplants for patients with induction failure or in relapse following HSCT.[22]

REDUCED-INTENSITY ALLOGENEIC HCT

A growing body of evidence is accruing from clinical studies of RIC with allogeneic HSCT for AML.[24-31] Overall, these data suggest that long-term remissions (two to four years) can be

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achieved in patients with AML who because of age or underlying comorbidities would not be candidates for myeloablative conditioning regimens. Meta-analyses, RCTs, and larger non-randomized studies are included below.

A 2014 meta-analysis compared reduced-intensity and myeloablative conditioning regimens for allogeneic HSCT in patients with AML.[32] The analysis included 23 clinical trials that were reported between 1990 and 2013, with approximately 15,000 adult patients. Eleven studies included AML and myelodysplastic syndrome (MDS) and five included AML only. A subanalysis from 13 trials in patients with AML or MDS showed that OS was comparable in patients who received either reduced-intensity or myeloablative transplants, and the two-year or less and two-year or greater OS rates were equivalent between the two groups. The two- to six-year PFS, non-relapse mortality, and acute and chronic graft-versus-host disease (GVHD) rates were reduced after RIC-HCT, but relapse rate was increased. Similar outcomes were observed regardless of disease status at transplantation. Among the RIC-HSCT recipients, survival rates were superior if patients were in complete remission at transplantation.

Solomon (2019) performed a retrospective cohort analysis to compare myeloablative and reduced intensity conditioning for AML (n=818), ALL (n=286), and MDS (n=221).[33] The primary end point was disease-free survival. Data from patients aged 18 to 70 treated at the Center for International Blood and Marrow Transplant Research (over 400 transplant centers worldwide) years received T-cell-replete bone marrow or peripheral blood from a haploidentical relative. An analysis that adjusted for comorbidity score, graft type, and disease risk index found that for younger patients (between the ages of 18 and 54 years), disease-free survival was lower with reduced-intensity regimens in. In older patients (between the ages of 55 and 70), disease-free survival did not differ between conditioning groups. In the younger patients, but not older patients, relapse was higher with reduced-intensity regiments in the adjusted analysis. Non-relapse mortality was not different based on conditioning regimen intensity in younger patients but was lower with reduced-intensity regimens in older patients. Overall survival was not different based on conditioning regimen intensity after adjusting for disease, comorbidity score, CMV seropositivity, and disease risk index. The authors concluded that myeloablative regimens are preferred and reduced-intensity regimens should be reserved for those unable to tolerate myeloablation.

A randomized comparative trial (Bornhauser 2012) in matched patient groups compared the net health benefit of allogeneic HSCT with reduced-intensity conditioning (RIC) versus myeloablative conditioning.[34] In this study, patients (age 18-60 years) were randomly assigned to receive either RIC (n=99) of four doses of 2 Gy of total-body irradiation and 150 mg/m^2 fludarabine or standard conditioning (n = 96) of six doses of 2 Gy of total-body irradiation and 120 mg/kg cyclophosphamide. All patients received cyclosporin and methotrexate as prophylaxis against graft-versus-host disease. The primary endpoint was the incidence of non-relapse mortality (NRM) analyzed in the intention-to-treat population. This unblinded trial was stopped early because of slow accrual of patients. The incidence of NRM did not differ between the RIC and standard conditioning groups (cumulative incidence at three years 13% [95% CI 6 to 21] versus 18% [10 to 26]; HR 0.62 [95% CI 0.30 to 1.31], respectively). Relapse cumulative incidence at three years was 28% [95% CI 19 to 38] in the RIC group and 26% [17 to 36]; HR 1.10 [95% CI 0.63 to 1.90]) in the standard conditioning group. Disease-free survival at 3 years was 58% (95% CI 49 to 70) in the RIC group and 56% ([46 to 67]; HR 0.85 [95% CI 0.55 to 1.32]) in the standard conditioning group. Overall survival at three years was 61% (95% CI 50 to 74) and 58% (47 to 70); HR 0.77 (95% CI 0.48 to 1.25) in the RIC and standard conditioning groups, respectively. No outcomes differed significantly

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between groups. Grade 3 to 4 of oral mucositis was less common in the RIC group than in the standard conditioning group (50 patients in the reduced-intensity conditioning group vs. 73 patients in the standard conditioning group); the frequency of other side-effects such as GVHD and increased concentrations of bilirubin and creatinine did not differ significantly between groups.

In a 2014 study, Bitan compared outcomes in children with AML who underwent allogeneic HSCT using RIC regimens or myeloablative conditioning regimens.[35] A total of 180 patients were evaluated, 39 who underwent RIC and 141 who received myeloablative regimens. Univariate and multivariate analyses showed no significant differences in the rates of acute and chronic GVHD, leukemia-free survival, and OS between treatment groups. The five-year probabilities of OS with RIC and myeloablative regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were not higher with RIC compared with myeloablative conditioning (MAC) regimens (39% vs 39%; p=0.95), and recipients of MAC regimens were not at higher risk for transplant-related mortality compared with recipients of RIC regimens (16% vs 16%; p=0.73).

Ringden (2013) published a phase II single-center, randomized toxicity study that compared MAC and RIC in allogeneic HSCT to treat AML.[36] Adult patients 60 years of age or younger with AML were randomly assigned (1:1) to treatment with RIC (n=18) or MAC (n=19) for allogeneic HSCT. A maximum median mucositis grade of 1 was observed in the RIC group compared with 4 in the MAC group (p<0.001). Hemorrhagic cystitis occurred in eight (42%) of the patients in the MAC group and none (0%) in the RIC group (p<0.01). Results of renal and hepatic tests did not differ significantly between the two groups. RIC-treated patients had faster platelet engraftment (p<0.01) and required fewer erythrocyte and platelet transfusions (p<0.001) and less total parenteral nutrition than those treated with MAC (p<0.01). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18) (p=0.02). Donor chimerism was similar in the two groups with regard to CD19 and CD33, but was delayed for CD3 in the RIC group. Five-year treatment- related morbidity was approximately 11% in both groups, and rates of relapse and survival were not significantly different. Patients in the MAC group with intermediate cytogenetic AML had a three-year survival of 73%, compared with 90% among those in the RIC group.

PRACTICE GUIDELINE SUMMARY

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines (v.3.2020) for acute myeloid leukemia are generally consistent with this policy.[1]

SUMMARY

There is enough research to show that allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen, or a reduced-intensity conditioning regimen may be medically necessary for people with acute myeloid leukemia (AML) when policy criteria are met. Additionally, autologous HCT may be considered medically necessary to treat AML for any indication other than as first line treatment.

Due to a lack of evidence and guidelines, autologous and allogeneic hematopoietic cell transplantation with any regimen is considered investigational when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)

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Codes	Number	Description
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.29

Hematopoietic Cell Transplantation for Breast Cancer

Effective: April 1, 2020

Next Review: January 2021
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Single autologous HCT is considered **not medically necessary** to treat any stage of breast cancer.

II. Tandem autologous HCT is considered **not medically necessary** to treat any stage of breast cancer.

III. Allogeneic HCT is considered **investigational** to treat any stage of breast cancer.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27

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POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease high-dose chemotherapy (with or without radiation) that is active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develop after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are

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limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

HCT IN SOLID TUMORS IN ADULTS

HCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental. Initial enthusiasm for the use of autologous transplant with the use of high-dose chemotherapy (HDC) and stem cells for solid tumors has waned with the realization that dose intensification often fails to improve survival, even in tumors with a linear-dose response to chemotherapy. With the advent of reduced-intensity allogeneic transplant, interest has shifted to exploring the generation of alloreactivity to metastatic solid tumors via a graft-versus-tumor effect of donor-derived T cells.

EVIDENCE SUMMARY

HISTORY OF HEMATOPOIETIC STEM-CELL TRANSPLANT FOR BREAST CANCER

In the late 1980s/early 1990s, initial results of phase II trials for breast cancer and autologous HCT were promising, showing high response rates in patients with metastatic disease who underwent high-dose consolidation, with a subset of up to 30% remaining disease-free for prolonged periods.[1] In the early 1990s, larger prospective comparisons of conventional-dose chemotherapy to high-dose therapy with SCT were initiated but accrued slowly, with up to a decade from initiation to the reporting of results.[1] The first results from randomized trials at a single institution in early stage and metastatic disease showed survival benefits, but were ultimately shown to be based on fraudulent data.[1] In the interim, though, the treatment became almost standard of care, while many patients received high-dose therapy off protocol, further reducing accrual to ongoing randomized trials.[1] The results of the randomized trials were presented beginning in 1999 and showed little survival benefit; subsequently, the number

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of HCT procedures performed for breast cancer decreased from thousands every year to only a few.[1]

AUTOLOGOUS STEM-CELL TRANSPLANT

Systematic Reviews

A meta-analysis by Wang (2012) included aggregate data from 14 trials (n = 5,747) published since March 2010.[2] Clinical trials of patients receiving HCT as a first-line treatment for primary breast cancer were eligible for inclusion. A higher treatment-related mortality was found among the patients who received HCT compared to standard chemotherapy (relative risk [RR] 3.42, 95% confidence interval [CI] 1.32 to 8.86). Overall survival did not differ significantly between groups, with a hazard ratio (HR) of 0.91 (95% CI 0.82 to 1.00) for the HCT compared to standard treatment. Risk of secondary, non-breast cancer was higher in the HCT group (RR 1.28, 95% CI 0.82 to 1.98). Disease-free survival was better in the HCT group compared to chemotherapy alone (RR 0.89, 95% CI 0.79 to 0.99). Patients receiving HCT had a greater risk of dying during remission than patients treated with nonmyeloablative chemotherapy due to the toxicity of the regimen. This increase in treatment-related mortality may help explain why there was no observed overall survival benefit for patients receiving HCT when disease-free survival was observed to be superior to standard chemotherapy.

Berry (2011) performed a meta-analysis with individual patient data from 15 randomized trials comparing autologous HCT with HDC (n = 3,118) to standard chemotherapy (n = 3,092) for patients with high-risk primary breast cancer.[3] A survival analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status. HCT was associated with a non-significant 6% reduction in risk of death (HR 0.94, 95% CI 0.87 to 1.02, p=0.13) and a significant reduction in the risk of recurrence (HR 0.87, 95% CI 0.81 to 0.93, p<0.001). Toxic death was higher in the HCT group with 72 (6%) of 1,207 deaths in these trial arms compared to 17 (1.4%) of 1,261 deaths in the standard therapy arms. In a subgroup analysis, the authors investigated whether age, number of positive lymph nodes, tumor size, histology, hormone receptor status, or human epidermal growth factor receptor 2 (HER2) status impacted survival when comparing HCT to standard treatment. The authors found that HER2-negative patients receiving HCT had a 21% reduction in the risk of death and HER2-negative and hormone receptor-negative patients receiving HCT had a 33% reduction in the risk of death. In their discussion, the authors state that this relationship could be spurious due to the amount of missing data on HER2 status and suggest that HCT is unlikely to show much benefit in these subgroups of patients.

Another systematic review by Berry (2011) included six randomized trials that compared the use of HDC with autologous HCT to control chemotherapy regimens in metastatic breast cancer.[4] Data from a total 866 women were pooled, and overall survival (OS) and progression-free survival (PFS) were assessed in a meta-analysis. While there was a significantly higher PFS in the HDC with HCT group, this did not translate into an OS benefit. A subgroup analysis failed to identify any patient groups that might derive benefit from this treatment.

A Cochrane systematic review and meta-analysis published in July 2005 pooled data from six randomized controlled trials (RCTs) on metastatic breast cancer reported through November 2004 (n = 438 randomized to autologous HCT, 412 to conventional dose therapy).[5] The risk of treatment-related mortality was significantly higher in the arm randomized to HCT (15 vs. 2 deaths, RR 4.07, 95% CI 1.39 to 11.88). Treatment-related morbidity also was more severe

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among those randomized to HCT. OS did not differ significantly between groups at one, three, or five years after treatment. Statistically significant differences in event-free survival at one year (RR 1.76, 95% CI 1.40 to 2.21) and five years (RR 2.84, 95% CI 1.07 to 7.50) favored the HCT arms. Only one of the six included trials had followed all patients for at least five years. Reviewers recommended further follow-up for patients randomized in the other five trials. They also concluded that, in the interim, patients with metastatic breast cancer should not receive HCT outside of a clinical trial, since available data showed greater treatment-related mortality and toxicity without improved overall survival.

A second Cochrane systematic review and meta-analysis, also published in July 2005, included data from 13 RCTs on patients with high-risk (poor prognosis) early breast cancer (n = 2,535 randomized to HCT, and 2,529 to conventional dose therapy).[6] Treatment-related mortality was significantly greater among those randomized to HDC with HCT (65 vs. 4 deaths, RR=8.58, 95% CI 4.13, 17.80). Treatment-related morbidity also was more common and more severe in the high-dose arms. There were no significant differences between arms in OS at any time after treatment. Event-free survival was significantly greater in the HCT group at three years (RR 1.12, 95% CI 1.06 to 1.19) and four years (RR 1.30, 95% CI 1.16 to 1.45) after treatment. However, the two groups did not differ significantly with respect to event-free survival at five and six years after treatment. Quality of life scores were significantly worse in the HCT arms than in controls soon after treatment, but differences were no longer statistically significant by one year. Reviewers concluded that available data were insufficient to support routine use of HCT for patients with poor-prognosis early breast cancer.

A systematic review and meta-analysis published in 2007 included RCTs comparing autologous HCT to standard dose chemotherapy in women with early, poor prognosis breast cancer, which included 13 trials to September 2006 with 5,064 patients.[7] Major conclusions were that at five years, event-free survival approached statistical significance for the high-dose group, but no OS differences were seen. There were more transplant-related deaths in the high-dose group. The end conclusion was that there was insufficient evidence to support routine use of autologous HCT for treating early, poor prognosis breast cancer.

Nieto (2009) performed a meta-analysis of all randomized trials published or updated since 2006 focusing on those that compared HDC with standard-dose chemotherapy for high-risk primary breast cancer.[8] The meta-analysis of 15 randomized trials involving patients with high-risk primary breast cancer or metastatic disease (n = 6,102) detected an absolute 13% event-free survival benefit in favor of HDC and autologous HCT (p=0.0001) at a median follow-up of six years. The absolute differences in disease-specific and overall survival did not reach statistical significance (7% and 5%, respectively). Subset analyses suggested that HDC could be particularly effective in patients with triple negative tumors (hormone receptor and HER2-negative). The authors concluded that HDC remains a valid research strategy in certain subpopulations with high-risk primary breast cancer, for example those with triple negative tumors.

Randomized Controlled Trials

There were no RCTs identified that were not included in the systematic reviews above.

Nonrandomized Studies

In 2013, the Italian Group of Bone Marrow and Hematopoietic Stem-Cell Transplantation and Cellular Therapy (GITMO) published registry data on 415 patients with metastatic breast

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cancer who received HDC and autologous HCT between 1990 and 2005.[9] More than 95% of the transplants performed used peripheral blood stem cells. Sixteen percent of patients received a tandem transplant. Estrogen-receptor (ER) status was known in 328 patients, 65% of whom were ER-positive. HER2 expression data were insufficient for subset analysis. After a median follow-up of 27 months (range 0 to 172 months), PFS at 5 and 10 years was 23% and 14%, and OS was 47% and 32%, respectively. The authors reported statistically significant survival benefit in patient subgroups including those with ER-positive tumors and those without visceral metastases; however, these are established positive prognostic factors. In addition, the authors did not report which patients received hormonal therapy, nor was it known if/which patients received targeted HER2 therapy, and it is unclear what impact on survival therapies other that HCT may have had.

In 2013, GITMO published registry data on the use of adjuvant HDC with autologous HCT in 1,183 patients with high-risk primary breast cancer (three or more involved lymph nodes), treated between 1990 and 2005.[10] Data on ER and HER2 status were available in 85% and 48% of patients, respectively. The majority of patients with hormone receptor-positive tumors received tamoxifen after HCT. The median lymph node involvement at surgery was 15 (range 4 to 63). Greater than 95% of the patients received peripheral blood-mobilized stem cells. After a median follow-up of 7.1 years, disease-free survival was 9.6 years, with 65% of patients free of disease at five years. Median OS was not reached, with 75% of patients alive at five years post-transplantation. Subgroup analysis showed significantly better OS in endocrine-responsive tumors and in patients who received multiple transplant procedures. Transplant-related mortality was 0.8% and late cardiac and secondary tumor-related mortality were approximately 1% overall.

Cheng (2017) compared long-term outcomes for inflammatory and non-inflammatory breast cancer (IBC, non-IBC) treated with HDC and autologous HCT, using data from the Center for International Blood & Marrow Transplant Research (CIBMTR).[11] A total of 3,387 patients from 91 centers, who underwent treatment between 1990 and 2002 and had sufficient follow-up data, were included in the study. There were 2,423 patients excluded due to lack of follow-up data. The majority of patients had non-IBC (n=2,860, 84.4%). At initial presentation, 84% of the 527 patients with IBC had stage III disease, and 80% of the non-IBC patients had high-risk, stage II/III disease. No differences were seen in transplant-related mortality, 1- and 10-year PFS, or OS between the those with stage III IBC and those with stage II/III non-IBC.

Additional retrospective and registry studies have reported outcomes in high-risk or metastatic breast cancer patients treated with HDC and autologous HCT.[12-15] As with other studies of breast cancer treatment, most of these have reported improved survival in patients with endocrine-responsive tumors relative to those with triple-negative.

TANDEM AUTOLOGOUS STEM-CELL TRANSPLANT

Kroger (2006) reported on the comparison of single vs. tandem autologous HCT in 187 patients with chemotherapy-sensitive metastatic breast cancer.[16] Only 52 of 85 patients completed the second HDC cycle in the tandem arm, mostly due to withdrawal of consent (most common reason), adverse effects, progressive disease, or death. The rate of complete remission was 33% in the single-dose arm versus 37% in the tandem arm (p=.48). Although there was a trend toward improved PFS after tandem HCT, median overall survival tended to be greater after single versus tandem HDC (29 vs. 23.5 months, respectively, p=0.4). The authors concluded that tandem HCT cannot be recommended for patients with chemotherapy-

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sensitive metastatic breast cancer because of a trend for shorter overall survival and higher toxicity compared with single HCT.

In a study that was included in the systematic reviews above, Schmid (2005) randomized 93 patients without prior chemotherapy for metastatic breast cancer to standard-dose chemotherapy or double HDC with autologous HCT.[17] The primary study objective was to compare complete response rates. Objective response rates for the patients in the HDC group were 66.7% versus 64.4% for the standard group (p=0.82). There were no significant differences between the two treatments in median time to disease progression, duration of response, or OS (OS 26.9 months vs. 23.4 months for the double high-dose arm versus the standard arm, respectively, p=0.60).

ALLOGENEIC STEM-CELL TRANSPLANT

To date, allogeneic HCT for breast cancer has mostly been used in patients who have failed multiple lines of conventional chemotherapy.[18]

Ueno (2008) reported the results of allogeneic HCT in 66 women with high-risk metastatic breast cancer from 15 centers who underwent transplantation between 1992 and 2000.[19] Thirty-nine (59%) received myeloablative and 27 (41%) reduced-intensity conditioning (RIC) regimens. A total of 17 (26%) patients had received a prior autologous HCT. Median follow-up time for survivors was 40 months (range 3 to 64 months). Treatment-related mortality was lower in the RIC group (7% vs. 29% at 100 days, p=0.03). PFS at one year was 23% in the myeloablative group versus 8% in the RIC group (p=0.09). Overall survival rates after myeloablative conditioning versus the RIC group were 51% (95% CI 36 to 67%) versus 26% (95% CI 11 to 45%, p=0.04) at one year, 25% (95% CI 13% to 40%) versus 15% (95% CI 3% to 34%, p=0.33) at two years, and 19% (95% CI 8% to 33%) versus 7% (95% CI <1% to 25%, p=0.21) at three years, respectively.

Fleskens reported the results of a Phase II study of 15 patients with metastatic breast cancer treated with HLA-matched reduced-intensity allogeneic HCT.[20] Median patient age was 49.5 years (range 39.7 to 60.8 years) and all patients had been extensively pretreated and had undergone at least one palliative chemotherapy regimen for metastatic disease. Treatment-related mortality was 2/15 (13%). One-year PFS was 20% and one- and two-year OS was 40% and 20%, respectively. The authors noted no objective tumor responses, but concluded that the relatively long PFS suggests a graft-versus-tumor effect.

PRACTICE GUIDELINE SUMMARY

The National Comprehensive Cancer Network guidelines do not address the use of HCT in the treatment of breast cancer.[21]

SUMMARY

There is enough research to show that autologous hematopoietic cell transplantation (HCT) does not improve survival in people with breast cancer. No clinical guidelines based on research recommend autologous HCT for people with breast cancer. Therefore, autologous HCT is considered not medically necessary for this indication.

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There is not enough research to show that allogeneic HCT can improve health outcomes for people with breast cancer. No clinical guidelines based on research recommend allogeneic HCT for people with breast cancer. Therefore, allogeneic HCT is considered investigational for the treatment of any breast cancer.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal

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Codes	Number	Description
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.30

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Effective: March 1, 2020

Next Review: September 2020
Last Review: January 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address non-Hodgkin lymphomas, chronic lymphocytic leukemia and small lymphocytic lymphoma, or Waldenstrom macroglobulinemia. These topics are considered separately in medical policies Transplant No. 45.23, 45.35, and 45.40, respectively.

I. A first autologous hematopoietic cell transplant for Hodgkin lymphoma may be considered **medically necessary** for any of the following:

   A. Primary refractory disease, defined as one or more of the following:

      1. Disease regression of less than 50 percent after four to six cycles of anthracycline-containing chemotherapy
      2. Disease progression during induction therapy

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3. Disease progression within 90 days after the completion of first-line treatment

B. Relapsed disease

II. Autologous hematopoietic cell transplantation for Hodgkin lymphoma is considered **investigational** for any of the following:

A. As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for newly diagnosed disease to consolidate a first complete remission; or

B. A second autologous hematopoietic cell transplantation after a prior autologous hematopoietic cell transplantation.

III. Allogeneic hematopoietic cell transplantation (using either reduced intensity conditioning [RIC] or myeloablative conditioning) for Hodgkin lymphoma may be considered **medically necessary** for any of the following:

A. Primary refractory disease, defined as any of the following:

1. Disease regression of less than 50 percent after four to six cycles of anthracycline-containing chemotherapy
2. Disease progression during induction therapy
3. Disease progression within 90 days after the completion of first-line treatment

B. Relapsed disease

C. Failed prior autologous hematopoietic cell transplantation used to treat primary refractory or relapsed disease

IV. A second allogeneic hematopoietic cell transplantation is considered **investigational** for the treatment of Hodgkin lymphoma.

V. Allogeneic hematopoietic cell transplantation is considered **investigational** as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for newly diagnosed Hodgkin lymphoma to consolidate a first complete remission.

VI. Tandem hematopoietic cell transplantation is considered **investigational** for the treatment of Hodgkin lymphoma**.**

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.

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- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

ALLOGENEIC DONORS

The ideal allogeneic donors are HLA-identical matched siblings. Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23
4. Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35
5. Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia, Transplant, Policy No. 45.40

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II gene loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of *allogeneic* HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to be delivered at doses that could otherwise not be given without stem cells, which are infused to "rescue" hematopoiesis after high dose therapy. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term "reduced-intensity conditioning" (RIC) will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

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HODGKIN LYMPHOMA

Hodgkin Lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2012, there were an estimated 9,060 new diagnoses and 1,190 deaths in the U.S.[1] Two distinct age groups are affected by this disease (indicating a bimodal distribution), those between the ages of 15 and 30 years, and, to a lesser extent, patients aged 55 and older.[2]

The 2008 World Health Organization (WHO) classification divides HL into two main types[3]; these classifications did not change in the 2016 update:[4]

- *Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)*
- *Classical Hodgkin lymphoma (CHL)*
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

In Western countries, CHL accounts for 95% of cases of HL and NLPHL, only 5%. Classic Hodgkin lymphoma is characterized by the presence of neoplastic Reed-Sternberg cells in a background of numerous non-neoplastic inflammatory cells. NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocytic and histiocytic cells termed “popcorn cells.”

The following staging system for HL recognizes the fact that the disease is thought to typically arise in a single lymph node and spread to contiguous lymph nodes with eventual involvement of extranodal sites. The staging system attempts to distinguish patients with localized HL who can be treated with extended field radiation from those who require systemic chemotherapy.

STAGING FOR HODGKIN LYMPHOMA

Staging for Hodgkin lymphoma is based on the Ann Arbor staging system. Patients with HL are generally classified into three groups: early-stage favorable (stage I–II with neither any B symptoms nor large mediastinal lymphadenopathy), early-stage unfavorable (stage I–II with large mediastinal mass, extranodal involvement, elevated erythrocyte sedimentation rate, involvement of three or more lymph node, or with B symptoms), and advanced-stage disease (stage III–IV). Each stage is subdivided into A and B categories. “A” indicates no systemic symptoms are present and “B” indicates the presence of systemic symptoms, which include unexplained weight loss of more than 10% of body weight, unexplained fevers, or drenching night sweats.[5]

Stage I

Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II

Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of lymph node regions involved should be indicated by a subscript (e.g., II2)

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Stage III
Involvement of lymph node regions or structures on both sides of the diaphragm. These patients are further subdivided as follows:

- III-1: disease limited to spleen or upper abdomen
- III-2: periaortic or pelvic node involvement

Stage IV
Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

HL is highly responsive to conventional chemotherapy; however, patients who prove refractory or who relapse after first-line therapy have a significantly worse prognosis. Primary refractory HL is defined as disease regression of less than 50% after 4–6 cycles of anthracycline-containing chemotherapy, disease progression during induction therapy, or progression within 90 days after the completion of first-line treatment.[6]

In patients with relapse, the results of salvage therapy vary depending upon a number of prognostic factors, as follows: the length of the initial remission, stage at recurrence, and the severity of anemia at the time of relapse.[7] Early and late relapse are defined as less or more than 12 months from the time of remission, respectively. Approximately 70% of patients with late first relapse can be salvaged by autologous HCT, but not more than 40% with early first relapse.[8]

Only approximately 25%-35% of patients with primary progressive or poor-risk recurrent HL achieve durable remission after autologous HCT, with most failures being due to disease progression after transplant. Most relapses after transplant occur within 1–2 years and once relapse occurs post-transplant, median survival is <12 months.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of Hodgkin lymphoma, comparative clinical trials that compare this therapy to standard medical treatment, such as treatment with standard chemotherapy regimens, are needed. Further, for treatment of hematologic cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR FRONT-LINE THERAPY OF HODGKIN LYMPHOMA

Two nonrandomized comparative studies, by Federico and Carella, have been published on the use of autologous HCT versus additional standard chemotherapy as front-line therapy for advanced or unfavorable HL patients.[9,10] Neither study found a difference in overall survival at five years, nor was a treatment difference observed in the study which followed patients for ten

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years following treatment allocation.[10] Both sets of authors concluded that their respective results did not support the use of autologous HCT over conventional chemotherapy for first-line treatment of HL.

AUTOLOGOUS HCT FOR RELAPSED/REFRACTORY DISEASE

Autologous HCT is widely considered the therapy of choice for relapsed and refractory HL. To date, two randomized controlled trials, and several nonrandomized studies have been published on the use of single autologous HCT for relapsed or refractory HL. Additional studies have been published on the use of a secondary autologous HCT; however the studies had significant limitations including an inappropriate comparison groups and heterogeneity in preparative regimens.

Systematic Reviews

In a 2013 Cochrane systematic review, Rancea investigated the best available treatment with high-dose chemotherapy (HDC) followed by autologous HCT for patients with relapsed or refractory HL after first-line treatment.[11] Authors included three trials with 14 publications which included 398 patients. Authors concluded a PFS benefit for patients with relapsed or refractory Hodgkin lymphoma after first-line therapy who were treated with HDC followed by autologous HCT compared to patients treated with conventional chemotherapy. In addition, authors determined a positive trend regarding OS, but more trials are needed to detect a significant effect. Further, authors concluded that intensifying the HDC regime before HDC followed by autologous HCT did not show a difference as compared to HDCT followed by autologous HCT, but was associated with increased adverse events.

A 2012 comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ) considered the use of autologous HCT in pediatric patients with relapsed or refractory disease.[2] Based upon available evidence (small, retrospective case series), the researchers concluded that, “Overall there appears to be a favorable risk-benefit profile for the treatment of Hodgkin’s disease with HCT in patients with progressive disease or relapse” and that among patients for whom autologous transplant is not an option, allogeneic transplant should be considered.

Randomized Controlled Trials (RCTs)

The British National Lymphoma Investigation (BNLI) study was the first to show a progression-free survival benefit with autologous HCT over conventional chemotherapy in relapsed or refractory HL patients.[12] Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20).[13] A significantly better event-free survival (EFS) at three years of 53% versus 10% was reported in the patients who underwent transplant versus the group that did not.

Subsequently, these findings were confirmed in a larger trial by the German Hodgkin Study Group (GHSG) and European Group for Blood and Marrow Transplantation (EBMT).[14] Patients relapsing after initial chemotherapy were randomized to chemotherapy without transplant or to autologous HCT. In the final analysis of 144 patients, freedom from treatment failure at three years was 55% in the transplanted group versus 34% in the nontransplanted group. This benefit was maintained in subgroup analysis, regardless of early or late relapse and the results were confirmed in follow-up data at seven years.[15]

Nonrandomized Studies

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Several large retrospective studies have reported EFS rates ranging from 25%–60%, with OS rates from 35%–66%, showing that disease status before autologous HCT was the most important prognostic factor for the final outcome.[6,16]

Limited treatment options exist for patients who relapse following an autologous HCT, and include single-agent palliative chemotherapy or occasionally, localized radiation therapy.[15] When a further remission may be attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than one year.[17] There is limited experience with second autologous HCT, and treatment-related mortality is high (25%–40%).[13] Smith and colleagues reported the outcomes of 40 patients (21 with HL and 19 with non-Hodgkin lymphoma [NHL]) who underwent a second autologous HCT for relapsed lymphoma.[18] Results reported were combined for the two populations, but the authors state that the outcomes of patients with HL and NHL were similar. Median age at second HCT was 38 years (range: 16–61). The second HCT was performed more than one year after the first in 82%. Treatment-related mortality at day 100 post-transplant was 11% (95% CI: 3–22%). At a median follow-up of 72 months (range: 12–124 months) after the second HCT, 73% of patients had died, 62% of these due to relapsed lymphoma. One-, three-, and five-year progression-free survival (PFS) probabilities were 50% (95% CI: 34–66%), 36% (95% CI: 21–52%) and 30% (95% CI: 16–46%), respectively. Corresponding OS probabilities were 65% (95% CI: 50–79%), 36% (95% CI: 22–52%), and 30% (95% CI: 17–46%), respectively. The authors stated that limitations to their study included the absence of an appropriate comparison group, and that it was not known how many patients were considered for a second HCT, but were unable to mobilize sufficient stem cells or were otherwise unable to proceed to the second transplant. Finally, they stated that the heterogeneity of the preparative regimens used in this population precluded comparison of efficacy.

While the above studies address Classic Hodgkin Lymphoma, only a limited number of studies have examined autologous HCT for relapsed/refractory nodular lymphocyte-predominant Hodgkin lymphoma. Among these is a recent retrospective study (Akhtar, 2018) with 60 patients that reported autologous HCT provided excellent disease control, with five-year PFS and OS of 66% and 87%, respectively.[19]

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR FRONT-LINE THERAPY OF HODGKIN LYMPHOMA

The application of allogeneic HCT (allo-HCT) as an initial therapy for the treatment of patients with HL appears limited, due to a high procedure-related mortality. No controlled trials evaluating allo-HCT as first-line treatment for HL were identified. In addition, systematic reviews of HCT for HL did not discuss studies on allo-HCT as first-line therapy.

ALLOGENEIC HCT FOR HL FOR RELAPSED/REFRACTORY DISEASE

In 2016, Rashidi reported results from a meta-analysis of allogeneic cell transplantation (allo-SCT) in HL patients with end points at six-month, one-, two-, and three-year relapse-free survival (RFS) and overall survival (OS).[20] Data were pooled from 42 studies including 1850 patients. The pooled estimates (95% confidence interval) for six-month, one-year, two-year and three-year RFS were 77 (59-91)%, 50 (42-57)%, 37 (31-43)% and 31 (25-37)%, respectively. The corresponding numbers for OS were 83 (75-91)%, 68 (62-74)%, 58 (52-64)% and 50 (41-58)%, respectively. The authors concluded that over time, outcomes related to allo-SCT for HL have improved; their analyses indicated to survival plateau. Heterogeneity was

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found within the pooled studies, and the authors concluded their results indicate a need for improved allo-SCT treatment strategies.

Elshenawy (2018) performed a survival analysis of patients with Hodgkin lymphoma who failed HDC and autologous HCT.[21] The authors analyzed 137 HL patients (out of 347 transplanted patients) who experienced post autologous SCT failure. The 27 patients included in the analysis who received a second HCT (15 allogeneic, 2 auto) or brentuximab had significantly longer OS than other treatments (50.6 versus 22.5 months; $p<0.027$).

Reduced-Intensity Conditioning

To date, most of the reduced-intensity conditioning (RIC) allogeneic HCTs have been performed in patients who have failed a previous autologous HCT for primary relapsed/refractory HL, and most of the studies are characterized by small numbers of patients, disparate preparative and graft-versus-host disease (GVHD) prophylaxis regimens, and varying lengths of follow-up. Examples of such studies include the following:

Gaudio (2019) retrospectively analyzed patients who received RIC allogeneic HCT for relapsed/refractory HL.[22] A total of 72 patients were include, of which 89% had had a previous autologous HCT. At 100 days post-transplant, 29 (43%) patients were in complete remission, 19 (28%) were in partial remission, 15 (22%) had stable disease, and 4 (6%) had progressive disease. Median follow-up was 48 months. Kaplan-Meier estimated five-year OS and PFS were 35% and 34%, respectively. Non-relapse mortality in the 20 months following transplant was 17%.

Sarina (2010) reported a retrospective study of 185 patients with HL who had failed an autologous HCT.[23] One hundred twenty-two had donors available for a salvage RIC allogeneic HCT; of these, 104 (85%) were transplanted. Sixty-three patients did not have a suitable donor and were treated with salvage chemotherapy or radiotherapy. Clinical characteristics between the two groups did not differ. After a median follow-up of 48 months, PFS and OS were better in the group that underwent the salvage allogeneic HCT (39.3% vs. 14.2% and 66% vs. 42%, respectively; $p<0.001$), showing a survival benefit of an RIC allogeneic HCT versus conventional treatment after a failed autologous HCT for HL. This study supports one of the policy statements for RIC HCT.

Peggs (2005) investigated outcomes with RIC allogeneic HCT and T-cell depletion in multiply relapsed patients.[24] Forty-nine patients were enrolled, 90% of whom had failed a previous autologous transplant. Primary study endpoints were engraftment, toxicity, non-relapse-related mortality, and graft-versus-host-disease (GVHD) incidence. All patients achieved engraftment. Thirty-one patients had an HLA-matched donor and 18 an unrelated donor. The cumulative incidence of non-relapse-related mortality was 4.1% at 100 days post-transplant and 16.3% at 730 days post-transplant. Patients with unrelated donors had a significantly higher non-relapse-related mortality (34% vs. 7%) at 730 days. Projected four-year OS and PFS were 56% and 39%, respectively.

Alvarez (2006) reported the results of a Spanish Cooperative Protocol using RIC allogeneic HCT in 40 patients with relapsed or refractory HL.[25] Seventy-three percent of patients had failed a previous autologous HCT. Thirty-eight patients received hematopoietic cells from an HLA-identical sibling. One-year treatment-related mortality was 25%. OS and PFS were 48% and 32%, at two years, respectively. For patients who had failed a previous autologous HCT,

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two-year OS and PFS were 75% and 70%, respectively, in the subset that relapsed more than 12 months after autologous HCT.

Todisco (2007) evaluated the efficacy of RIC allogeneic HCT in 14 patients with refractory or progressive HL after high-dose chemotherapy and autologous HCT.[17] All of the patients had received at least one prior course of HDC, and 50% had undergone two previous courses. The median time from the first and second courses of HDC and the RIC allogeneic HCT was 15 and 8 months, respectively (range 2–34 and 2–31 months). With a median follow-up of 21 months post-RIC allogeneic HCT (range 3–74 months), 10 of the 14 patients were alive. Estimated OS at one and two years was 93% and 73%, respectively, for the entire population; 83% and 44%, respectively, for patients with chemotherapy-resistant disease; and 100% for those with chemotherapy-sensitive disease.

The European Group for Blood and Marrow Transplantation (EBMT) published the results of the outcomes of 89 HL patients with relapsed or refractory disease who received a RIC allogeneic HCT and were compared to 79 patients who received myeloablative conditioning.[26] Sixty-two percent of the RIC-group had undergone a previous autologous HCT versus 41% of the patients in the myeloablative group. Although the incidence of relapse was nearly double in the RIC group (57% vs. 30%), after a median follow-up for surviving patients of 75 months (range, 12 to 120 months), 24 in the RIC group (26.9%) and 18 in the conventional group (22.8%) were alive. Five-year OS was 22% (95% CI: 13–31%) for the conventional group and 28% (95% CI: 18–38%) for the RIC group. Independent adverse prognostic factors for OS were a previously failed autologous HCT (RR=1.59; 95% CI: 1.07 to 2.35; p=0.02), the use of myeloablative conditioning (RR=1.62; 95% CI, 1.27 to 3.29; p=0.04), and the presence of refractory disease (RR=1.51; 95% CI: 1.03–2.21; p=.003).

Anderlini (2008) published the results of 58 patients from one institution with relapsed/refractory HL who received uniform conditioning regimens for RIC allogeneic HCT.[27] Fifty-seven percent of patients received their allograft from an unrelated donor. Eighty-three percent of patients had failed a prior autologous HCT. Projected two-year OS and PFS rates were 64% (range: 49%–76%) and 32% (range: 20%-45%), with two-year disease progression/relapse at 55% (43%–70%). There were no statistically significant differences in OS, PFS, or disease progression/relapse between matched related and unrelated donor transplants.

Sureda (2012) reported the results of a phase II study of 92 patients with relapsed HL and an HLA-identical sibling, a matched unrelated donor, or a one antigen mismatched, unrelated donor who were treated with salvage chemotherapy followed by RIC allogeneic transplantation.[28] Fourteen patients had refractory disease and died from progressive lymphoma with a median OS after trial entry of 10 months (range, 6-17 months). Seventy-eight patients proceeded to allograft (unrelated donors, n=23). Fifty were allografted in complete or partial remission and 28 in stable disease. Non-relapse mortality rate was 8% at 100 days and 15% at one year. Relapse was the major cause of failure. The PFS rate was 47% at one year and 18% at four years from trial entry. For the allografted population, the PFS rate was 48% at one year and 24% at four years. Chronic graft-versus-host disease was associated with a lower incidence of relapse. Patients allografted in complete remission had a significantly better outcome. The OS rate was 71% at one year and 43% at four years.

A 2007 non-systematic review of the role of allogeneic HCT in HL by Laport summarizes the results of the recent studies of the use of RIC allogeneic HCT for HL as follows: most patients

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have failed a prior autologous HCT and are therefore heavily pretreated going into the RIC allogeneic HCT; chemotherapy sensitivity is a reliable predictor of outcome; a matched versus an unmatched related donor did not affect survival in most reports; and approximately one-third to one-half of these patients may be cured with RIC allogeneic HCT.[29]

Despite the nonrandomized nature of available studies on allogeneic HCT in patients with relapsed/refractory HL, comparative estimates of treatment effect are sufficient to suggest reduced non-relapse mortality and some suggest a graft-versus-HL effect with favorable disease control in these poor-prognosis patients. Retrospective comparisons of myeloablative vs reduced-intensity conditioning suggest an improvement in outcomes, including OS when RIC is used. Until randomized prospective trials are done, RIC conditioning is preferable in this setting.

TANDEM (AUTOLOGOUS-AUTOLOGOUS) HCT

Several pilot studies have evaluated the role of tandem autologous HCT in treatment of HL:

Smith (2018) reported results of noncomparative study of tandem autologous HCT for relapsed/refractory HL.[30] Of 98 enrolled patients, 89 received the first transplant and 82 patients received both transplants and were included in the final analysis. The interval between day zero of the first and second transplant was between 28 and 60 days and the median follow-up was 5.4 years. There were no treatment-related deaths and 15 total deaths. The two-year and five-year PFS were 63% (95% CI 52 to 72%) and 55% (95% CI 44 to 64%) and two-year and five-year OS were 91% (95% CI 83 to 95%) and 84% (95% CI, 74% to 90%). Authors concluded that these results were promising compared to historical controls.

Morschhauser (2008) reported on the results of a multicenter prospective trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HCT in 245 patients with relapsed/refractory HL.[31] Median follow-up time was 51 months (range: 20–110 months). Patients were categorized as poor risk (n=150) if they had primary refractory disease (n=77) or two or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV disease at the time of relapse, or relapse occurring within previously irradiated sites (n=73). Poor risk patients were eligible for tandem autologous transplants. Intermediate-risk patients (n=95), defined as one risk factor at relapse, were eligible for a single transplant. Overall, 70% of the poor-risk patients received tandem transplants and 97% of the intermediate-risk patients received a single transplant.

Overall, 94 poor-risk patients responded to cytoreductive chemotherapy (partial or complete response [PR or CR]) whereas 55 patients had chemotherapy-resistant disease. A total of 137 patients (including the 94 patients with chemotherapy-sensitive disease and 43 of 55 with chemotherapy–resistant disease) received the first autologous HCT. Among 121 patients who were fully restaged, 64 patients had achieved a CR, 37 a PR, and four had stable disease. These 105 patients then underwent the second autologous HCT after a median of 65 days. Among them, 80 patients achieved a CR, including 17 patients who had achieved PR and three patients with stable disease after the first transplant. Among the 55 patients who had cytoreduction failure, 30 responded to the first transplant (nine with CR), and 17 achieved CR after the second transplant.

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Outcome analysis based on the intent-to-treat sample showed five-year freedom from second failure and OS were 73% and 85% for the intermediate-risk group and 46% and 57% for the poor-risk group, all respectively.

Fung (2007) reported results from a pilot study to evaluate the toxicities and efficacy of tandem autologous HCT in patients with primary refractory or poor risk recurrent HL.[32] The study involved 28 patients with primary progressive and 18 with recurrent HL who were enrolled into the study between April 1998 and March 2000. Patients had at least one of the following poor prognostic factors: first complete remission less than 12 months, extranodal disease, or B symptoms at relapse. Forty-one patients (89%) received the second transplant. With a median follow-up of 5.3 years (1.6-8.1), the five-year OS and PFS were 54% (95% CI: 40–69%) and 49% (95% CI: 34–63%), respectively.

Ferme (2002) reported that poor-risk patients who underwent tandem transplant and had a complete response to cytoreduction chemotherapy did not have superior outcomes compared to complete responders receiving a single transplant in previous studies.[33] However, poor-risk patients who were partial responders who underwent tandem transplants did better when compared to partial responders who received a single transplant in previous studies. In this study, five-year OS rates for poor-risk patients who completed the tandem transplant were 79% and 73% for complete and partial responders, whereas in a previous trial of single autologous HCT, five-year OS rates were 86% and 37% for complete and partial responders, respectively.[33] The authors concluded that a single autologous HCT is appropriate for intermediate-risk patients and for poor-risk patients who are complete responders to cytoreductive chemotherapy, but that tandem autologous HCT showed a benefit in patients with chemotherapy-resistant disease and in partial responders to cytoreductive conditioning.

The evidence regarding the use of tandem transplant for Hodgkin lymphoma includes a small number of non-randomized studies. Due to the low incidence and quick progression of poor-risk HL disease, random assignment of single versus tandem autologous HCT may not be a viable research option. However, given the small number of studies and the efficacy of other treatments following transplant, further research is needed to demonstrate that the benefits of tandem transplant outweigh the risks. Therefore, the data on tandem transplants is insufficient to determine outcomes with this type of treatment.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

Guidelines from the National Comprehensive Cancer Network (NCCN) offer the following on the use of HCT in HL:[5] In CHL patients with refractory disease, high dose therapy and autologous stem cell rescue is included as an additional therapy option. Additionally:

> Allotransplant is an option in select patients as a category 3 recommendation. Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

AMERICAN COLLEGE OF RADIOLOGY

In 2016, the American College of Radiology issued an Appropriateness Criteria on recurrent HL.[34] The criteria stated that while salvage therapy followed by autologous HCT is standard of care for relapsed HL, alternative therapies may be considered in select patients. For example,

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there is evidence that in patients with small isolated relapses occurring more than three years after initial presentation, a course of radiotherapy or combined modality therapy without autologous HCT may be considered. Also, radiotherapy may be considered as part of combined modality therapy for patients with local relapse after treatment with chemotherapy alone or for relapses outside of the original site of disease.

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, guidelines were published by the American Society for Blood and Marrow Transplantation (ASBMT) on indications for autologous and allogeneic HCT.[35] Recommendations are intended to describe the current consensus on use of HCT within and outside of the clinical trial setting. Recommendations on Hodgkin lymphoma are provided in Table 1.

Table 1: ASBMT Recommendations for Hodgkin Lymphoma

Indication	Allogeneic HCT	Autologous
Adult		
First complete response (PET-)	N	N
First complete response (PET+)	N	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Pediatric		
First complete response	N	N
Primary refractory, sensitive	C	C
Primary refractory, resistant	C	N
First relapse, sensitive	C	C
First relapse, resistant	C	N
Second or greater relapse	C	C

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

In 2015, the ASBMT published the recommendations of their task force on the role of cytotoxic therapy with HCT in patients with Hodgkin Lymphoma.[36] Selected recommendations are shown in Table 2.

Table 2: Selected ASBMT Recommendations on Cytoxic Therapy with HCT for Hodgkin Lymphoma

Recommendation	Grade of Recommendation	Highest Level of Evidence
Autologous HCT		
ASCT should not be offered as first-line therapy for advanced disease	A	1+
ASCT should be offered as first-line therapy for patients who fail to achieve CR	B	2++
ASCT should be offered as salvage therapy over nontransplantation (except	A	1+

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localized disease or in patients with low-stage disease)		
ASCT should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy	B	2++
Tandem ASCT is not routinely recommended in standard-risk patients	C	2+
Allogeneic HCT		
Allo-HCT should be used for relapse after ASCT instead of conventional therapy	B	2++
RIC is the recommended regimen intensity	B	2++
All donor sources can be considered	A	1+
There are limited data for tandem ASCT/Allo-HCT	D	4
Allo-HCT is preferred over ASCT as second HCT (except in late relapse)	C	2+

ASCT: Autologous stem cell transplant; Allo-HCT: Allogeneic HCT; CR: Complete response; RIC: Reduced intensity conditioning

SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

There is enough research to show that in patients with relapsed or refractory Hodgkin lymphoma, autologous hematopoietic cell transplantation (HCT) leads to improved survival and freedom from failure compared with conventional chemotherapy. Therefore, in these patients, autologous HCT may be considered medically necessary.

Available research suggests that neither an autologous hematopoietic cell transplantation (HCT) as first-line treatment for Hodgkin lymphoma nor a second autologous HCT following a prior autologous HCT improve survival outcomes and are therefore considered investigational.

ALLOGENEIC HCT

The early research for allogeneic hematopoietic cell transplantation (HCT) as a treatment for patients with Hodgkin lymphoma (HL) shows high procedure-related mortality. Most of the reduced intensity conditioning allogeneic HCTs have been performed in patients who have failed a previous autologous HCT for primary relapsed/refractory HL. Most of the studies are characterized by small numbers of patients, differences in treatment approaches, and varying lengths of follow-up. However, the research has shown a reduction in mortality, and some studies suggest favorable disease control and possible cure, in these poor-prognosis patients. Therefore, in patients who have relapsed or refractory HL, allogeneic HCT may be considered medically necessary.

Due to high risk of treatment-related mortality, allogeneic hematopoietic cell transplantation (HCT) as a first-line treatment of Hodgkin lymphoma and subsequent allogeneic HCT *after* a previous allogeneic HCT are considered investigational**.**

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TANDEM HCT

The research shows that in some patients with relapsed or refractory Hodgkin lymphoma (HL), tandem autologous hematopoietic cell transplantation (HCT) may provide a survival benefit compared with single autologous HCT. More research is needed to know for sure. No clinical guidelines based on research recommend tandem HCT for patients with HL. Therefore, in these patients, the use of tandem transplantation is considered investigational.

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37. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Cell Transplantation for Hodgkin Lymphoma." Policy No. 8.01.29

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition

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	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.31

Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia

Effective: December 1, 2019

Next Review: August 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic hemopoietic cell transplantation may be considered **medically necessary** as a treatment of chronic myelogenous leukemia using either of the following regimens (A. or B.):
   A. Myeloablative conditioning regimen (see Policy Guidelines).
   B. Reduced-intensity conditioning (RIC) regimen in patients who meet clinical criteria for an allogeneic hemopoietic cell transplantation but who are not considered candidates for a myeloablative conditioning allogeneic hemopoietic cell transplantation (see Policy Guidelines).

II. Autologous hematopoietic cell transplantation is considered **investigational** as a treatment of chronic myelogenous leukemia.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

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POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

REDUCED-INTENSITY CONDITIONING

Patients who meet criteria for allogeneic hemopoietic cell transplantation but whose advanced age (typically older than 60 years) and existing comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude the use of a standard myeloablative conditioning regiment, may be considered candidates for *reduced-intensity conditioning (RIC).*

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- If patient requires a reduced-intensity conditioning (RIC) regimen – documentation supporting reasons patient is unable to tolerate a standard myeloablative conditioning regimen

CROSS REFERENCES

1. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
2. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
3. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
4. Allogeneic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Transplant, Policy No. 45.24

BACKGROUND

Chronic myelogenous leukemia (CML) is a hematopoietic cell disorder that is characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22.

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HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

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Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is not only to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) is a hematopoietic cell disorder that is characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22. This cytogenetic change results in constitutive activation of BCR-ABL, a tyrosine kinase (TK) that stimulates unregulated cell proliferation, inhibition of apoptosis, genetic instability, and perturbation of the interactions between CML cells and the bone marrow stroma only in malignant cells. CML accounts for approximately 15% of newly diagnosed cases of leukemia in adults and occurs in about 1 to 2 cases per 100,000 adults.[1]

The natural history of the disease consists of an initial (indolent) chronic phase, lasting a median of 3 years, which typically transforms into an accelerated phase, followed by a "blast crisis," which is usually the terminal event. Most patients present in chronic phase, often with nonspecific symptoms that are secondary to anemia and splenomegaly. CML is diagnosed based on the presence of the Philadelphia chromosome abnormality by routine cytogenetics, or by detection of abnormal BCR-ABL products by fluorescence in situ hybridization or molecular studies, in the setting of persistent unexplained leukocytosis. Conventional-dose chemotherapy regimens used for chronic-phase disease can induce multiple remissions and delay the onset of blast crisis to a median of 4 to 6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors.

Drug therapies for chronic phase CML were limited to nonspecific agents, including busulfan, hydroxyurea, and interferon-alpha.[1] Imatinib mesylate (Gleevec®), a selective inhibitor of the abnormal BCR-ABL TK protein, is considered the treatment of choice for newly diagnosed CML. While imatinib can be highly effective in suppressing CML in most patients, it is not curative and is ineffective in 20% to 30%, initially or due to development of BCR-ABL mutations that cause resistance to the drug. The overall survival (OS) of patients who present in chronic phase is greater than 95% at two years and 80% to 90% at five years.[2] Two other TK inhibitors (TKIs; dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) to treat CML following failure or patient intolerance of imatinib. In any case, allogeneic HCT remains the only treatment capable of inducing durable remissions or cure in CML patients.

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For patients who progress on imatinib, the therapeutic options include increasing the imatinib dose, changing to another TKI, or allo-HCT. Detection of BCR-ABL mutations may be important in determining an alternative TKI; the presence of T315I mutation is associated with resistance to all TKIs and should indicate the need for allo-HCT or an experimental therapy. In any case, allogeneic HCT remains the only treatment capable of inducing durable remissions or cure in CML patients. TKIs have been associated with long-term remissions; however, if progression occurs on TKI therapy, allo-HCT is generally indicated and offers the potential for cure.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of chronic myelogenous leukemia, comparative clinical trials that compare this therapy to standard medical treatment, such as treatment with a TKI, or among patients not able to tolerate TKIs, or for whom TKIs fail, standard conditioning regimens, are needed. Further, for treatment of hematologic cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

ALLOGENEIC HCT

Allogeneic hematopoietic cell transplantation (HCT) is the only known potentially curative therapy for chronic myelogenous leukemia (CML), and has been accepted as a standard treatment. It became a standard of treatment for CML in the 1980's when the graft-versus-leukemia (GVL) effect was shown to be the critical factor for long-term disease control.[3] Studies in patients with chronic phase disease who received an HLA-matched sibling donor transplant had a 45%–75% probability of long-term disease-free survival, while those transplanted with more advanced disease had a 15%–40% long-term survival.[4] Young, good-risk patients who received transplants early in the chronic phase from HLA-matched but unrelated donors had a 40%–60% chance of long-term survival, which was lower than that of similar patients transplanted from matched sibling donors.[5,6]

Allogeneic HCT was once commonly performed for the treatment of CML; with the advent of TKIs, this has changed. A retrospective analysis of data from the Center for International Blood and Marrow Transplant Research Center (CIBMTR) showed that transplantation for CML was in decline prior to U.S. Food and Drug Administration (FDA) approval of imatinib in 2001.[7] Subsequently, long-term follow-up results from the International Randomized Study of Interferon and STI 571 (IRIS) of imatinib mesylate, plus the availability of two additional approved TKI agents (nilotinib and dasatinib), have caused modification of the timing of application of allogeneic cell transplant.[8-10] This procedure now is typically delayed in patients with newly diagnosed CML, who will receive imatinib mesylate as front-line treatment. It also may only be used early when a complete molecular response to the drug fails or is not achieved soon after starting imatinib administration. The currently-available evidence suggests that TKI-pretreatment does not lead to worse outcomes if HCT is needed. Techniques for

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allogeneic HCT have continued to develop, with important advancements in the use of nonmyeloablative or reduced-intensity conditioning (RIC) preparative regimens.

Systematic Review

A 2012 comparative effectiveness review published by the Agency for Healthcare Research and Quality (AHRQ) on the use of HCT in the pediatric population considered allogenic HCT for the treatment of CML.[11] The review cited the risk of disease relapse with interruption in TKI therapy, which complicates the decision to proceed to allogeneic HCT. The review concluded that there is no evidence to inform the "decision and timing to proceed to allogeneic HCT" following treatment with TKI therapy.

Randomized Controlled Trials

In a prospective, randomized controlled trial (RCT) comparing primary HCT from a matched family donor (n=166) with best available drug treatment (n=261), which enrolled patients from 1997 to 2004, there were no differences in overall survival between groups (10-year survival 0.76 for HCT patients vs 0.69 for best available drug treatment patients).[12] Those with low transplant risk treated with HCT had improved survival compared with those treated with medical therapy, but after patients entered blast crisis, survival did not differ between groups.

Nonrandomized Studies

Chhabra (2018) performed a retrospective analysis of data from the Center for International Blood and Marrow Transplant Research database to compare RIC and myeloablative conditioning.[13] The analysis included 1395 patients that received RIC (n = 191) or MAC (n = 1204) allo-HCT for CML. Patients in blast phase at transplant and alternative donor transplants were excluded from the analysis. There was no statistically significant difference between groups for the primary outcome, OS. Leukemia-free survival and nonrelapse mortality also did not differ significantly between groups. However, there were statistically significant differences in cumulative incidence of chronic graft-versus-host disease (lower with RIC, hazard ratio (HR), 0.77; p = .02) and risk of early relapse after allo-HCT (higher with RIC, HR 1.85; p = 0.001).

Zhang (2016) retrospectively compared imatinib (n=292) and allo-HCT (n=141) in patients with CML.[14] Survival rates were significantly longer in the imatinib group than in the allo-HCT group: five-year EFS rates were 84% and 75% ($p<0.05$) and five-year OS rates were 92% and 79%, both respectively. Findings were similar for patients with chronic phase and advanced phase disease.

Overall, among nine studies compiled in a non-systematic review by Chakrabarti (2007), outcomes achieved with RIC allogeneic transplants have been similar to those with conventional allotransplants, with overall survival (OS) rates ranging from 35% at 2.5 years to 85% at five years among patients in chronic phase 1 at transplant.[15] Among the studies included in this review, treatment-related mortality or nonrelapse mortality (NRM) ranged from 0% at one year to 29% at one year. In the largest experience, a retrospective European Group for Blood and Marrow Transplantation (EMBT) study of 186 patients, overall survival (OS) was 54% at three years using a variety of RIC regimens in patients in chronic phase 1 (n=118), chronic phase 2 (n=26), acute phase (n=30), and blast crisis (n=12).[16] Among patients transplanted in the first chronic phase (CP1), OS was 69% at three years.

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Xu (2015) retrospectively compared second-generation TKI therapy with allo-HCT in 93 patients with accelerated-phase CML.[17] The second-generation TKI therapy group included 33 subjects, most of whom had been previously treated with another TKI (n=31 with imatinib and n=2 with nilotinib). Of 60 patients treated with allo-HCT, 10 were treated with primary HCT and 50 had been previously treated with imatinib. Median OS was significantly shorter with second-generation TKI treatment than with allo-HCT (22 months vs 82 months). Median progression-free and event-free survival (EFS) rates were similarly shorter with second-generation TKI treatment than with allo-HCT.

Several studies have compared outcomes for CML patients treated with allo-HCT in the pre- and current TKI eras. While these studies generally report no worsening in treatment outcomes for allo-HCT following TKI therapy, they are limited by the underlying differences in treatment regimens of different eras. In a retrospective analysis by Shen (2015), of 106 patients who underwent allo-HCT who either did (n=36) or did not (n=70) receive prior treatment with TKIs, no significant difference was reported in 10-year relapse-free survival or OS.[18] However, TKI-treated patients had a higher incidence of 0.5-year transplant-related mortality. In another retrospective analysis comparing patients treated with allo-HCT in the pre-TKI era (1989-2001; n=39) with those treated in the TKI era (2002-2013; n=30), Chamseddine (2015) reported longer three-year OS and leukemia-free survival among patients treated in the TKI era.[19]

Warlick (2012) recently reported outcomes of 306 patients with CML treated with myeloablative or RIC preparative regimens before allogeneic HCT at the Center for International Blood and Marrow Transplant Research.[20] Although age, disease status, prior treatment (including TKI and autologous transplant), and strength of donor match differed between the treatment groups, a statistical model indicated a potential association between use of RIC preparatory regimen and increased survival (when compared with traditional myeloablative regimens). However, the lack of randomization to treatment group limits the interpretation of these findings as treatment imbalances between groups may have accounted for the differences seen in survival rates.

The optimal timing for HCT in the context of TKI therapy is still being evaluated. Liu (2013) evaluated outcomes for chronic-phase CML patients who underwent HCT after imatinib failure.[21] The study authors retrospectively evaluated 105 patients with newly diagnosed chronic-phase CML seen at a single institution from 1999 to 2011. A total of 66 patients received first-line imatinib therapy, 26 (treated before 2003) received interferon followed by imatinib, and 13 received front-line allo-HCT with curative intent. A total of 22 (21.0%) patients received allo-HCT overall, including 13 as front-line therapy and 9 following imatinib failure. Compared with those who received front-line allo-HCT, those who underwent HCT following imatinib failure had higher European Group for Blood and Bone Marrow Transplantation (EBMT) risk score (p=0.03). Among patients receiving allo-HCT (n=22), patients with imatinib failure and disease progression had a significantly worse OS (p=0.015) compared with those receiving allo-HCT as front-line therapy (median follow-up, 134 months, range, 6-167 months). One patient died of relapse and one of chronic GVHD among patients receiving front-line allo-HCT, with a three-year survival rate of 91.7% (95% confidence interval [CI], 29 to 38 months).

In addition to the comparative studies, a number of case series, primarily involving a single center, have reported outcomes for patients treated with allo-HCT following TKI treatment failure. In a series of 51 patients treated with allo-HCT, 32 of whom were treated for TKI resistance or intolerance, eight-year OS and EFS were 68% and 46%, respectively.[22] A prospective series of 28 patients who underwent allo-HCT after failure of at least two TKIs

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reported deep molecular remission in 18 subjects.[22] However, all six patients transplanted in blast crisis died. In a smaller series, Zhao (2014) reported outcomes for 12 patients with CML with disease progression on imatinib who were primary disease and three of transplant-related complications.[23] After a median follow-up of 28 months (range, 12-37 months) after HCT, 8/12 (66.7%) patients were alive, including seven with complete molecular remission.

Lee (2014) attempted to identify predictors of outcomes in patients who underwent allogeneic HCT for CML in chronic phase.[24] Ninety-seven patients were included, 47 of whom were TKI-naïve and 50 of whom had received one or more TKI therapy before HCT. Most (N=48) of the TKI-recipients had received imatinib as initial therapy; two had received second-generation TKIs (dasatinib, bosutinib). After a median follow-up of 115.8 months, four-year OS and event-free survival were 80.4% and 58.8%, respectively. Multivariate analysis showed that there were no differences in survival outcomes based on prior TKI therapy. However, in multivariate models, age at transplant was significantly associated with relapse and transplant-related mortality, while graft source (peripheral blood vs bone marrow) was significantly associated with event-free survival. The authors conclude that their findings confirm prior researchers' findings that pretreatment with imatinib does not affect survival outcomes after allogeneic HCT for CML.

In addition to being used before HCT, TKI therapy may be used after HCT to prevent or treat disease relapse. Egan (2015) conducted a retrospective analysis of patients at a single institution who underwent allogeneic HCT for CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) at a single institution with detectable BCR-ABL transcripts and RNA available for sequencing of the ABL kinase domain in both the pre- and post-HCT settings to evaluate the impact of pre-HCT mutations in the ABL kinase domain on post-HCT relapse.[25] Among 95 patients with CML with available polymerase chain reaction transcripts, 10 (10.5%) were found to have pre-HCT ABL kinase mutations known to confer resistance to TKIs. Of those with CML, 88.4% underwent myeloablative chemotherapy and 11.6% underwent nonmyeloablative chemotherapy. A total of 29 CML patients received post-HCT TKIs, 19 (65.5%) for prophylaxis and 10 (34.5%) for treatment of refractory or relapsed disease. In 9 (64.2%) of the 14 patients with pre-HCT mutations (both CML and Philadelphia chromosome –positive ALL), the same mutation conferring TKI resistance was also detectable after HCT. Among the 14 with pre-HCT mutations, 8 (57.1%) received a TKI in the post-HCT setting, and seven (50%) demonstrated post-HCT refractory disease or relapse. Of the seven with relapsed disease, five had been given a predictably ineffective TKI based on mutation status in the first 100 days after HCT. RIC regimens have many of the same limitations as standard-intensity conditioning: relapse, graft-versus-host disease (GVHD; particularly chronic GVHD), and mortality from treatment-related causes other than myelotoxicity. However, in the absence of prospective, comparative, randomized trials, only indirect comparisons can be made between the relative clinical benefits and harms associated with myeloablative and RIC regimens with allogeneic HCT. Comparison of study results is further compromised by heterogeneity among patients, treatments, and outcome measures. Nonetheless, clinical evidence suggests outcomes in CML are similar with myeloablative and RIC allogeneic HCT.[10,15,16]

However, the advent of TKI therapy has altered the treatment paradigm for CML such that the majority of patients are treated initially with a TKI until disease progresses. While progression may occur within months of starting a TKI, this may be delayed for years, as shown by the results of the IRIS trial[8] and other studies.[9,10] With the addition of two other TKIs (dasatinib and nilotinib) plus the possibility of effective dose escalation with imatinib to override

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resistance, it is possible to maintain a typical CML patient past the upper age limit (usually 50–55 years) at which a myeloablative allogeneic HCT is considered an option.[8,26,27] In such cases, RIC allogeneic HCT would be considered a viable choice because it harnesses the potent GVL effect of allogeneic HCT with substantially reduced treatment-related morbidity and mortality compared to myeloablative allogeneic HCT.

AUTOLOGOUS HCT

A major limitation in the use of autologous HCT in patients with CML is the risk that leukemic cells will be re-infused. However, it is recognized that many CML patients still have normal marrow stem cells. Techniques used to isolate and expand this normal clone of cells have included ex vivo purging, long-term culture, and immunophenotype selection.[28] Even without such techniques, there have been isolated case reports of partial cytogenetic remissions after autologous HCT, and one study has suggested that patients undergoing such therapy may have improved survival compared with historical controls.[4]

In 1994, McGlave summarized the results of 200 consecutive autologous transplants using purged or unpurged marrow from eight different transplant centers.[29] Of the 200 patients studied, 125 were alive at a median follow-up of 42 months. Of the 142 transplanted in chronic phase, the median survival had not been reached at the time of publication, while the median survival was 35.9 months for those transplanted during an accelerated phase. Other data consist of small, single institution case series using a variety of techniques to enrich the population of normal stem cells among the harvested cells.[4] Additional reports of small, uncontrolled studies with a total of 182 patients (range: 15–41 patients) given autotransplants for CML included patient populations that varied across the studies. Some focused on newly diagnosed patients or those in the first year since diagnosis.[30,31] Others focused on patients who did not respond to or relapsed after initial treatment using interferon alfa,[32,33] or who received interferon alfa as maintenance therapy following autologous HCT.[34] Finally, some focused on patients transplanted in the late chronic phase[35] or after transformation to accelerated phase or blast crisis.[36] Although some patients achieved complete or partial molecular remissions and long-term disease-free survival, these studies do not permit conclusions free from the influence of patient selection bias. Note also that all autotransplanted patients included in these reports were treated before imatinib mesylate or newer TKIs became available. Since these agents have been shown to induce major hematologic and, less often, cytogenetic remissions, even among patients in accelerated phase and blast crisis, future studies of autotransplants for CML may focus on patients who fail or become resistant to imatinib mesylate. Alternatively, it may be incorporated into combination regimens used for high-dose therapy.[37]

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, guidelines by the American Society for Blood and Marrow Transplantation addressed indications for autologous and allogeneic HCT for CML.[38] Recommendations are listed in Table 1.

Table 1. ASBMT Recommendations on Allogeneic and Autologous HCT for CML

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Indications	Allogeneic HCT	Autologous HCT
Pediatric		
Chronic phase	C	N
Accelerated phase	C	N
Blast phase	C	N
Adult		
Chronic phase, TKI intolerant	C	N
Chronic phase, TKI refractory	C	N
Chronic phase 2+	S	N
Accelerated phase	S	N
Blast phase	S	N

ASBMT: American Society for Blood and Marrow Transplantation; C: Standard of care, clinical evidence available, CML: chronic myeloid leukemia; HCT: hematopoietic cell transplantation; N: Not generally recommended; S: standard of care; TKI: tyrosine kinase inhibitor.

NATIONAL COMPREHENSIVE CANCER NETWORK

Current National Comprehensive Cancer Network (NCCN) guidelines for chronic myeloid leukemia (v2.2020) recommend allogeneic HCT for those with advanced phase CML at presentation or disease progression to blast phase.[39] The guidelines also state outcomes of allogeneic HCT are dependent on age and comorbidities, donor type, and transplant center.

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

SUMMARY

There is enough research to show that patients with chronic myelogenous leukemia (CML) may have improved overall health outcomes when treated with allogeneic hematopoietic cell transplantation (HCT) in select patient subgroups. Clinical practice guidelines based on research also recommend allogeneic HCT for CML. Thus, myeloablative conditioning followed by allogeneic HCT may be considered medically necessary for these patients. Among patients who are not candidates for a myeloablative conditioning regimen, allogeneic HCT with a reduced-intensity conditioning (RIC) regimen may also be considered medically necessary.

There is not enough research to show that autologous HCT improves health outcomes in patients with chronic myelogenous leukemia (CML) over alternative treatments such as tyrosine kinase inhibitors (TKIs). Compared to alternatives, the risks associated with myeloablative autologous HCT outweigh the benefits. Therefore, autologous HCT in patients with chronic myelogenous leukemia (CML) is considered investigational.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest, with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion

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	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.32

Hematopoietic Cell Transplantation for Autoimmune Diseases

Effective: August 1, 2020

Next Review: April 2021
Last Review: June 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplant has been proposed as a treatment for autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis/scleroderma.

MEDICAL POLICY CRITERIA

I. Hematopoietic cell transplantation may be considered **medically necessary** as a treatment of systemic sclerosis/scleroderma if all of the following criteria are met (A. – H.):
   A. Transplant is an autologous hematopoietic cell transplant; and
   B. Patient is 18 to 60 years of age; and
   C. Condition has been present less than or equal to 5 years; and
   D. Modified Rodnan Scale Scores greater than or equal to 15; and
   E. Internal organ involvement, as indicated by one or more of the following:
      1. Cardiac: abnormal electrocardiogram; or
      2. Pulmonary involvement, as indicated by one or more of the following:

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a. Diffusing capacity of carbon monoxide (DLCo) <80% of predicted value; or
b. Decline of forced vital capacity (FVC) of >10% in last 12 months; or
c. Pulmonary fibrosis; or
d. Ground glass appearance on high resolution chest CT; or

3. Renal: scleroderma-related renal disease

F. History of < 6 months treatment with cyclophosphamide; and

G. No active gastric antral vascular ectasia; and

H. All of the following are met (1. – 7.):

1. Left ventricular ejection fraction >50%
2. Tricuspid annular plane systolic excursion >1.8 cm
3. Pulmonary artery systolic pressure <40 mm Hg
4. Mean pulmonary artery pressure <25 mm Hg
5. DLCo >40% of predicted value
6. FVC >45% of predicted value
7. Creatinine clearance of >40 ml/min

II. Autologous and allogeneic hematopoietic cell transplantation is considered **investigational** as a treatment of systemic sclerosis/scleroderma when Criterion I. is not met.

III. Autologous and allogeneic hematopoietic cell transplantation is considered **investigational** as a treatment of autoimmune diseases, including, but not limited to:

A. Autoimmune hepatitis and cryptogenic cirrhosis

B. Behçet's disease

C. Chronic inflammatory demyelinating polyneuropathy (CIDP)

D. Crohn's Disease

E. Diabetes mellitus, type I

F. GI autoimmune diseases including Crohn's disease, ulcerative colitis, and celiac disease

G. Immune cytopenias including but not limited to: autoimmune hemolytic anemia, Evans' s syndrome, immune thrombocytopenia, pure red cell or white cell aplasia, and thrombotic thrombocytopenia purpura

H. Immune vasculitis

I. Juvenile idiopathic arthritis

J. Multiple sclerosis (MS)

K. Neuromyelitis optica

L. Relapsing polychondritis

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M. Rheumatoid arthritis (RA)

N. Systemic lupus erythematosus (SLE)

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart notes
- Diagnosis and indication for transplant
- Measures of organ involvement, as outlined in the Policy Criteria

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

BACKGROUND

AUTOIMMUNE DISEASES

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, with some of the most common types being multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis/scleroderma.

The pathogenesis of autoimmune diseases is not well understood but appears to involve underlying genetic susceptibility and environmental factors that lead to loss of self-tolerance, culminating in tissue damage by the patient's own immune system (T cells).

Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (e.g., RA, SLE, and scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs. However, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

HCT in autoimmune disorders raises the question of whether ablating and "resetting" the immune system can alter the disease process and sustain remission, and possibly lead to cure.[1] Certain hematologic malignancies, aplastic anemia, and inborn errors of metabolism are treated with HCT.[1] However, its usage in autoimmune diseases has only been performed in approximately 1,000 patients in the last decade.[1]

The rationale for HCT for autoimmune disease is based on studies in experimental animal models, and on observations of remissions of autoimmune disease in patients who received

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HCT for hematologic malignancies.[2]

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT, previously referred to in this policy as hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome six. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

AUTOLOGOUS CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES

The goal of autologous HCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablative) and generate new self-tolerant lymphocytes.[3] This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablative), as is often performed in autologous HCT for hematologic malignancies.[3] However, there is currently no standard conditioning regimen for autoimmune diseases and both lymphoablative and myeloablative regimens are used.[1] The efficacy of the different conditioning regimens has not been compared in clinical trials.[1]

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the GVHD associated with allogeneic transplant, and the need to administer post-transplant immunosuppression after an allogeneic transplant.[1]

ALLOGENEIC CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES

The experience of using allogeneic HCT for autoimmune diseases is currently limited,[1] but has two potential advantages over autologous transplant. First, the use of donor cells from a genetically different individual could possibly eliminate genetic susceptibility to the autoimmune disease and potentially result in a cure. Second, there exists a possible graft-versus-autoimmune effect, in which the donor T cells attack the transplant recipient's autoreactive immune cells.[1]

EVIDENCE SUMMARY

Ideally, for autologous and/or allogeneic hematopoietic cell transplant (HCT) to be considered as a treatment for autoimmune disease, comparative studies with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects, and to

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establish guidelines regarding the timing of hematopoietic cell transplant. In order to establish guidelines for conditioning regimens, clinical studies that compare these therapies are also needed.

VARIOUS DISEASES

A systematic review prepared by the BCBSA TEC Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) evaluated the use of HCT among pediatric patients (age 21 or younger) with various medical conditions (cancer, metabolic disease or autoimmune disease).[4] Despite the lack of consistency in reported health outcomes and the rarity of randomized controlled trials, the review found that moderate-level evidence existed to support the association between single autologous HCT and "extended periods of drug-free clinical remission" among patients with newly diagnosed type 1 juvenile diabetes, and severe, refractory juvenile idiopathic arthritis, systemic lupus, systemic sclerosis, and Crohn's disease. Nevertheless, the review concluded that "The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies) of single autologous or allogeneic HCT versus conventional therapy or disease natural history in patients with newly diagnosed type 1 diabetes mellitus, or those with severe, refractory, poor prognosis autoimmune diseases, including: systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, Evans syndrome, autoimmune hemolytic anemia, and autoimmune cytopenia." The review recommended that additional controlled trials of adequate duration are required to evaluate the net benefit of HCT among pediatric patients with autoimmune disease.

A report from the British Society of Blood and Marrow Transplantation (BSBMT) data registry reported on long-term health outcomes of patients with one or more autoimmune diseases treated with autologous or allogeneic HCT from 1997 to 2009.[5] Data for 69 patients were reported (representing less than 1% of the total number of patients treated with HCT in the United Kingdom in that time period). One and five-year rates of overall survival (OS) were estimated at 85% and 78%, respectively, for patients treated with autologous transplantation, and 87% and 65%, respectively, for patients treated with allogeneic transplantation. Younger age at transplantation and lack of a connective tissue disorder (such as systemic lupus erythematosus) were associated with improved outcomes. Nevertheless, the authors caution that these results "should be viewed in the context of translational and developmental phases of this approach [HSCT] to poor prognosis and refractory autoimmune disease." They recommend the increased adoption of HSCT for individuals with autoimmune disease, but advocate that this take place in "prospective clinical studies in centres with a special interest."

MULTIPLE SCLEROSIS

Systematic Reviews

A systematic review and meta-analysis by Ge (2019) evaluated the long-term safety and efficacy of autologous HCT for multiple sclerosis (MS). [6] A total of 18 studies met inclusion criteria and included a total of 732 patients. Mean follow-up after HCT ranged from 19 months to 6.7 years and the number of patients ranged from 14 to 145. Four studies used high-intensity conditioning regimens. The progression-free survival (PFS) was 75% (95% confidence interval [CI] 0.69 to 0.81). The estimated treatment-related mortality was 1.34%

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(95% CI, 0.39 to 2.30), and the overall mortality was 3.58%. Subgroup analyses showed that factors associated with higher PFS were low- and intermediate-intensity regiments and relapsing remitting MS. Treatment-related mortality was 3.13% in patients receiving high-intensity conditioning.

Sormani (2017) conducted a systematic review and meta-analysis on the use of autologous HCT for the treatment of patients with severe treatment-refractory MS.[7] The studies differed in types and intensities of conditioning regimens used before HCT: low (n=2), intermediate (n=7), high (n=4), and mixed (n=2). Quality assessment of included studies was not discussed. Rate of progression at two and five years were calculated, as well as treatment-related mortality (defined as number of deaths within 100 days of transplant/number of transplants) and overall mortality (defined as total number deaths/number of patient-years). A total of 764 patients were included in the meta-analysis. The pooled proportion of patients with no evidence of disease activity at two years was 83% (range 70% to 92%) and at five years was 67% (range 59% to 70%). Pooled treatment-related mortality was 2.1% (95% CI 1.3 to 3.4) and overall mortality was 1.0% (95% CI 0.7 to 1.5)

A 2011 systematic review by Reston evaluated the safety and efficacy of autologous HCT in patients with progressive MS refractory to conventional medical treatment.[8] Eight small case series which monitored progression-free survival (PFS) with a median follow-up of at least two years were included. An additional six studies were included for a summary of mortality and morbidity. There was substantial heterogeneity across the eight case series. The majority of patients (77%) had secondary progressive MS, although studies also included those with primary progressive, progressive-relapsing, and relapse-remitting disease. Numbers of patients across studies ranged between 14 and 26. The studies differed in the types and intensities of conditioning regimens used prior to HCT, with five studies using an intermediate-intensity regimen, while the other three used high-intensity regimens. All of the studies were rated of moderate quality. The estimated rate of long-term PFS of patients receiving intermediate-intensity conditioning regimen was 79.4% (95% CI 69.9 to 86.5%) with a median follow-up of 39 months, while the estimate for patients who received a high-dose regimen was 44.6% (95% CI 26.5 to 64.5%) at a median follow-up of 24 months. Of the 14 studies that reported on adverse events, 13 were case series; from these, a total of seven treatment-related deaths were recorded; six non-treatment-related deaths occurred, five associated with disease progression.

A meta-analysis by Li (2016) found significant heterogeneity in 12 studies of HCT for MS.[9] At 12-months follow-up, there was a statistically significant decrease in the EDSS scores of patients compared to baseline (-0.62; 95% CI, -0.14 to -1.12). The authors concluded that while there was evidence that suggested a clinical benefit to this treatment, studies were limited by small sample sizes, and randomized controlled trials were needed.

Randomized Controlled Trials

Burt (2019) conducted a randomized controlled trial (RCT) comparing nonmyeloablative HCT with disease modifying therapy.[10] The study included 110 patients with relapse-remitting MS, with 98 patients evaluated at one year. Inclusion criteria were a minimum of two relapses while receiving disease modifying therapy in the last year or one relapse and at a separate time in the past 12 months the presence of MRI gadolinium-enhancing lesion(s), and an Expanded Disability Status Scale (EDSS; score range, 0-10, where 10 = worst neurologic disability) score of 2.0 to 6.0. Patients were randomized into two groups, those receiving disease modifying

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therapy and those receiving HCT. Patients could crossover from disease modifying therapy to HCT at one year if they experienced progression of disability. The primary outcome was disease progression, which was defined as an EDSS score of increase after at least one year of 1.0 point or more on two evaluations six months apart. Disease progression occurred in three patients who received HCT and 34 patients in the group receiving disease modifying therapy. Other measures reported included changes in EDSS scores, which improved from 3.38 to 2.36 in the HCT group and worsened from 3.31 to 3.98 in the disease modifying therapy group.

Nonrandomized Studies

Muraro (2017) reported long-term outcomes after autologous HCT for MS in a large, multi-center cohort.[11] This study included patients that were treated between 1995 and 2006 that had sufficient data for analysis, including the Expanded Disability Status Scale (EDSS) score at baseline, information on conditioning and graft methods, and at least one follow-up report after transplant. Data for 281 patients were obtained from 25 centers in 13 countries. The majority (218/281) of patients had progressive MS. Overall, the five-year probability of progression-free survival (by EDSS score) was 46% (95% CI, 42% to 54%) and total survival was 93% (95% CI, 89%-96%). Disease progression after transplant was associated with increased age (hazard ratio [HR], 1.03; 95% CI, 1.00 to 1.05), progressive as opposed to relapsing form of MS (HR, 2.33; 95% CI, 1.27 to 4.28), and three or more previous disease-modifying therapies (HR, 1.65; 95% CI, 1.10 to 2.47). A lower baseline EDSS score was associated with improved overall survival (HR, 2.03; 95% CI, 1.40 to 2.95).

Atkins (2016) tested a regimen of strong immunosuppression followed by autologous HCT in a phase II single-arm trial at three Canadian hospitals.[12] This study included 24 patients, aged 18-50, with a baseline EDSS score of 3.0 to 6.0 and a poor prognosis. The primary outcome was disease activity-free survival, and the median follow-up time was 6.7 years (range, 3.9-12.7). At three years after transplant, the proportion with disease activity-free survival was 69.6% (95% CI 46.6 to 84.2). After up to 13 years of post-transplant follow-up, 35% of patients had durable improvements in their EDSS score, and the rate of brain atrophy in patients decreased to that seen in healthy individuals. One patient died due to transplant complications.

Burman (2017) conducted a registry-based study of autologous HCT for pediatric MS patients.[13] Using data from the European Society for Blood and Marrow Transplantation registry, 21 patients were identified, with a median follow-up of 2.8 years. Of these, 16 (76%) had improved EDSS scores and two patients had a disease relapse. There were also two incidences of severe transplant-related toxicity, but neither were fatal.

A single-center case series by Burt (2015) reported on 151 patients, 123 with relapsing-remitting MS and 28 with secondary progressive MS.[14] Patients were treated with nonmyeloablative HCT between 2003 and 2014. Six patients were not included in the outcome analysis. The remaining 145 patients were followed for a median of two years (range, six months to five years). There were no treatment-related deaths. The primary outcome was change in the EDSS score. A decrease of at least 1.0 point was considered significant improvement and an increase of at least 1.0 point was considered significant progression. There was statistically significant improvement in EDSS score for the group as a whole compared with the pretransplant mean score of 4.0, decreasing to a mean EDSS score of 2.5 at three, four, and five years. In post hoc analysis, patients most likely to have statistically

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significant improvements in EDSS score were those with relapsing-remitting MS, with duration of disease of ten years or less, and those without sustained fever during HCT.

A multicenter case series by Burman (2014) reported on 48 patients with aggressive relapsing-remitting MS, defined as disease with high relapse frequency, and who failed conventional therapy.[15] Patients underwent autologous HCT. At the five-year follow-up, relapse-free survival was 87% and the EDSS score PFS (EDSS deterioration of <0.5 points) was 77%. The rate of disease-free survival (no relapses, no new MRI lesions, no EDSS score progression) was 68%. There was no mortality. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%).

Burt (2009) transplanted 21 patients with relapsing-remitting MS with ongoing relapses during treatment with interferon.[16] The conditioning regimen was nonmyeloablative. With a median follow-up of 37 months, 16 patients remained free of relapse, whereas 17 of the 21 patients had a one-point or greater improvement in their EDSS scores.

Guimaraes (2010) studied quality of life in 34 MS patients. At one year post transplantation, 27 (79%) patients showed stabilization or neurological improvement and statistically significant improvement in all domains of health-related quality of life.[17]

The European Society for Blood and Marrow Transplantation (EBMT) autoimmune diseases working party database published results on a retrospective study of 178 patients with MS who underwent autologous HCT.[18] After median follow-up of 42 months, the disease remained stable or improved in 63% of the group. In sub-group analysis, autologous HCT was found to be associated with significantly better progression-free survival in younger patients (i.e., younger than 40 years of age) with severe, progressive MS diagnosis compared to those older than 40 years. However, the authors caution that the role of autologous SCT in the treatment of refractory MS needs to be established through prospective randomized, controlled trials. Several editorials concur with the view that the role of autologous HCT is not established in MS or other autoimmune diseases.[19-21]

Fassas (2011) reported the long-term results of a Phase I/II study conducted in a single center that investigated the effect of HCT in the treatment of MS.[22] The authors reported on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HCT after a median follow-up period of 11 (range 2-15) years. Disease PFS at 15 years was 44% for patients with active central nervous system (CNS) disease and 10% for those without (p=0.01); median time to progression was 11 years (95% CI: 0 to 22) and two years (0 to 6). Improvements by 0.5 to 5.5 (median 1) Expanded Disability Status Scale (EDSS) points were observed in 16 cases lasting for a median of two years. In nine of these patients, EDSS scores did not progress above baseline scores. Two patients died, at two months and 2.5 years, from transplant-related complications. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HCT. The authors concluded that HCT should be reserved for aggressive cases of MS, still in the inflammatory phase of the disease, and for the malignant form, in which it can be life-saving, and that HCT can result in PFS rates of 25% and can have an impressive and sustained effect in suppressing disease activity on MRI.

Shevchenko (2012) reported the results of a prospective Phase II open-label single-center study which analyzed the safety and efficacy of autologous HCT with reduced-intensity conditioning regimen in 95 patients with different types of MS.[23] The patients underwent early,

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conventional, and salvage/late transplantation. The efficacy was evaluated based on clinical and quality-of-life outcomes. No transplantation-related deaths were observed. All of the patients, except one, responded to the treatment. At long-term follow-up (mean 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated PFS at five years was 92% in the group after early transplant versus 73% in the group after conventional/salvage transplant (p=0.01). No active, new, or enlarging lesions in MRI were registered in patients without disease progression. All patients who did not have disease progression were off therapy throughout the post-transplantation period. HCT was accompanied by a significant improvement in quality of life with statistically significant changes in the majority of quality-of-life parameters (p<0.05). A 2015 publication reported on 64 patients participating in this study who had at least 36 months follow-up. Thirty of the 64 patients (47%) improved at least 0.5 points on the EDSS scale compared to baseline.[24] Among the other patients, 29 (45%) were stable and five (7%) experienced worsening disease.

Mancardi (2012) reported their experience with 74 consecutive patients with MS treated with autologous HCT with an intermediate intensity conditioning regimen in the period from 1996 to 2008.[25] Clinical and MRI outcomes were reported. The median follow-up period was 48.3 months (range=0.8-126). Two patients (2.7%) died from transplant-related causes. After five years, 66% of patients remained stable or improved. Among patients with a follow-up longer than one year, eight out of 25 subjects with a relapsing-remitting course (31%) had a 6 to 12 months confirmed EDSS improvement >1 point after HCT, as compared with one out of 36 (3%) patients with a secondary progressive disease course (p=0.009). Among the 18 cases with a follow-up longer than seven years, eight (44%) remained stable or had a sustained improvement, while 10 (56%), after an initial period of stabilization or improvement with a median duration of 3.5 years, showed a slow disability progression.

Bowen (2012) reported the long-term safety and effectiveness of high-dose immunosuppressive therapy followed by autologous HCT in advanced MS.[26] Neurologic examinations, brain MRI and cerebrospinal fluid (CSF) for oligoclonal bands (OCB) were serially evaluated. There were 26 patients with a mean EDSS of 7.0; 17 with secondary progressive MS, eight with primary progressive, and one with relapsing/remitting. Median follow up was 48 months after HCT. The 72-month probability of worsening ≥1.0 EDSS point was 0.52 (95% CI: 0.30 to 0.75). Five patients had an EDSS at baseline of ≤6.0; four of them had not failed treatment at last study visit. OCB in CSF persisted with minor changes in the banding pattern. Four new or enhancing lesions were seen on MRI, all within 13 months of treatment. In this population with high baseline EDSS, a significant proportion of patients with advanced MS remained stable for as long as seven years after transplant. Non-inflammatory events may have contributed to neurologic worsening after treatment. HCT may be more effective in patients with less advanced relapsing/remitting MS.

In a small, phase II, RCT (n=21), Mancardi (2015) reported results of the effect of HCT compared with mitoxantrone on disease variables in patients with severe MS. [27]. Patients were randomized to either receive intense immunosuppression with a combination of drug therapy, followed by HCT or mitoxantrone (20 mg) every six months. The primary outcome measure was the total number of new T2 lesions during four years of follow-up. Results demonstrated that HCT reduced the total number of new T2 lesions compared with mitoxantrone (rate ratio, 0.21; P=0.00016). However, rates of disability did not change in either group. Hence, the clinical significance of the reduction in T2 lesions is unclear.

A small case series[28] evaluated patients with relapsing-remitting MS (n=123) or progressive

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MS (n=28), who were followed for up to five years. Patients were treated with cyclophosphamide and alemtuzumab (n=22) or cyclophosphamide and thymoglobulin (n=129), followed by HCT infusion. The primary outcome was the change in disability (measured by the Expanded Disability Status Scale [EDSS]). A mean follow-up of 2.5 years, results showed that EDSS scores improved significantly (P<0.001 at each follow-up assessment). In addition, there was significant improvement in disability in a total of 41 patients at two years (50%; 95% CI, 39% to 61%) and in a total of 23 patients at four years (64%; 95% CI, 46% to 79%). The relapse-free survival at four years was 80%s and the progression-free survival was 87%. Secondary measures of quality of life (QOL) also showed significant improvement from baseline. Study authors emphasized that although significant improvements were observed in neurological disability, randomized and comparative trials are necessary to confirm these findings.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Leone (2018) conducted a systematic review of clinical and laboratory studies using autologous HCT for patients with systemic lupus erythematosus (SLE).[29] The literature search, conducted through 2014, identified 25 studies (n=279 patients): 2 prospective, 10 retrospective, and 13 case reports. Quality assessment of included studies was not discussed in the publication. Heterogeneity between studies was high (I2=87%). The only pooled analysis conducted was on five studies reporting deaths, resulting in an overall mortality of 8.3% in a mean followup of 36 months.

Burt (2018) reported on 30 patients with refractory, chronic, corticosteroid dependent SLE who underwent autologous HCT.[30] Outcomes were measured at six months and yearly through five years. Disease remission was achieved by 24 patients. The SLE Disease Activity Index and quality of life (SF-36) improved significantly at each followup compared with baseline. No treatment-related mortality was reported. Five grade 4 and 60 grade 3 adverse events were reported.

Cao (2017) reported on 22 patients with SLE who underwent autologous peripheral blood HCT.[31] At five-year followup, PFS was 68% and overall survival was 95%. At last followup, 10 patients had relapsed. Adverse events included infections, secondary autoimmunity, lymphoma, and malignancy. The authors noted a difficulty in distinguishing between conditions caused by relapse or by the transplantation.

A systematic review by Leone (2017) evaluated the use of HCT in SLE and antiphospholipid syndrome (APS).[29] The authors found 25 studies that met inclusion criteria, with a total of 279 SLE patients, 54 of whom also had APS. While most of these studies reported improvements after HCT, one study found no benefit to transplant compared with immunosuppression alone. There were 32 out of 44 patients with APS were able to discontinue anticoagulation following transplantation. However, the authors noted a relatively high rate of adverse events, including 86 infections (30.8%), with three that were fatal.

Burt (2006) published the results of a prospective case series on the use of autologous HCT as salvage treatment in 50 patients (mean age 30; 43 women, seven men) with SLE refractory to standard care.[32] Patients underwent autologous SCT following a lymphoablative conditioning regimen and primary outcomes consisted of overall survival (OS) and disease-free survival. Treatment-related mortality was 4% (2/50) and after a mean follow-up of 29 months (range, six months to 7.5 years), estimated five-year survival was 84%, and the

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estimated probability of disease-free survival at five years was 50%. The investigators suggest these results justify a randomized trial comparing immunosuppression plus autologous HCT versus continued standard of care. An editorial by Petri and Brodsky that accompanied this article concurred that randomized clinical trials are needed to determine whether this treatment approach improves outcomes when compared with conventional therapies.[33]

A report from the EBMT Autoimmune Disease Working Party on the variables associated with development of a secondary autoimmune disease following autologous HCT in a group of 347 patients (with various primary autoimmune diseases) identified SLE as a risk factor for this complication (using multivariate analysis).[34] This finding points to the need for prospective, randomized, controlled trials to identify factors pre-disposing patients, specifically those with SLE, to development of a secondary autoimmune disease.

SYSTEMIC SCLEROSIS/SCLERODERMA

Systematic Reviews

Shouval (2018) conducted a meta-analysis of four studies (three RCTs and one retrospective comparative study) on the use of autologous HCT compared with cyclophosphamide alone for the treatment of systemic sclerosis.[35] Quality assessment of the three RCTs found that two of the RCTs had low risk in the randomization methods and outcome reporting, one RCT was unclear in randomization methods, and all three were high risk since blinding of patients and outcome assessors was not conducted. Meta-analyses of the RCTs showed that all-cause mortality favored HCT (risk ratio 0.6 [95% CI: 0.4 to 0.9]) and treatment-related mortality favored cyclophosphamide alone (risk ratio 10.8 [95% CI: 1.4 to 85.7]).

Host (2017) conducted a systematic review of autologous HCT for the treatment of systemic sclerosis.[36] The literature search, conducted through March 2016, identified nine studies (two RCTs and seven observational studies) for inclusion. The RCTs reported improvements in progression- and event-free survival and all studies reported improvements in modified Rodnan Skin Score. However, TRM rates ranged from 0% to 23%, with higher rates found with higher doses of cyclophosphamide or myeloablative conditioning regimens. No pooled analysis was conducted.

Randomized Controlled Trials

Sullivan (2018) conducted an RCT comparing autologous HCT with cyclophosphamide for the treatment of scleroderma.[37] Adult patients with scleroderma with maximum duration five years, active interstitial lung disease and scleroderma-related renal disease were eligible. The trial was originally designed for 226 patients, but due to low accrual, a total of 75 patients participated. Patients were randomized to receive total body irradiation (800 cGy), cyclophosphamide (120 mg/kg), equine antithymocyte globulin (90 mg/kg), and autologous HCT (n=36) or 12 monthly treatments with intravenous pulsed cyclophosphamide (n=39). Of the 36 patients randomized to receive HCT, 27 completed the trial per protocol (three died and six withdrew prematurely). Of the 39 patients randomized to receive cyclophosphamide alone, 19 completed the trial per protocol (11 died and 9 withdrew prematurely).

The primary outcome was a global rank composite score. This score does not measure disease activity or severity, but performs a pairwise comparison of the following: death, EFS, FVC, Disability Index of the Health Assessment Questionnaire, and the modified RSS. There were more percent pairwise comparisons favoring HCT over cyclophosphamide alone at 4 and

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4.5 years followup. The following disease progression events were significantly higher among patients receiving cyclophosphamide alone: initiating disease-modifying antirheumatic drugs, congestive heart failure leading to treatment, and pulmonary arterial hypertension. The following disease progression events were not significantly different among the two treatment groups: arrhythmia, pericardial effusion, renal crisis, and myositis. Death or respiratory, renal, or cardiac failure occurred in 28% and 51% of HCT and cyclophosphamide patients, respectively, at four years (p=0.06). Death from any cause occurred in 17% and 11% of HCT and cyclophosphamide patients, respectively, at four and a half years (p=0.28).

The results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in June 2014.[38] ASTIS was a Phase III RCT conducted in 10 countries at 29 centers with access to an EBMT-registered transplant facility. A total of 156 patients were recruited between March 2001 and October 2009. Individual patients were eligible if they were between 18 and 65 years of age; had diffuse cutaneous systemic sclerosis according to American Rheumatism Association criteria, with maximum duration of four years; minimum modified Rodnan skin score (mRSS) of 15 (range, 0 to 51 with higher scores indicating more sever skin thickening); and, involvement of heart, lungs, or kidneys. Patients were randomly allocated to receive high-dose chemotherapy (intravenous cyclophosphamide 200 mg/kg over four consecutive days and intravenous rabbit antithymocyte globulin 7.5 mg/kg total dose over three consecutive days) followed by CD34+ selected autologous HCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m2). Median follow-up was 5.8 years (interquartile range, 4.1 to 7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in mRSS, organ function, body weight, and quality-of-life scores.

A total of 53 primary end point events were recorded: 22 in the HCT group (19 deaths and three irreversible organ failures; eight patients died of treatment-related causes in the first year, nine of disease progression, one of cerebrovascular disease, one of malignancy) and 31 in the control group (23 deaths and eight irreversible organ failures [seven of whom died later]; 19 patients died of disease progression, four of cardiovascular disease, five of malignancy, two of other causes). The data show patients treated with HCT experienced more events in the first year but appeared to have better long-term event-free survival than the controls, as the Kaplan-Meier curves for overall survival (OS) cross at about two years after treatment with OS at that time estimated at 85%. According to data from the Kaplan-Meier curves, at five years, OS was an estimated 66% in the control group and about 80% the HCT group (p value unknown). Time-varying hazard ratios (modeled with treatment x time interaction) for event-free survival were 0.35 (95% CI, 0.15 to 0.74) at two years and 0.34 (95% CI, 0.16 to -0.74) at four years, supporting a benefit of HCT versus pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HCT group compared with 30 (37% by intention-to-treat, p=0.002).

The internal validity (risk of bias) of ASTIS was assessed according to the United States Preventive Services Task Force (USPSTF) criteria for randomized trials. The study was rated as “poor” quality according to this framework because it has two major flaws: outcome assessment was not masked to patients or assessors, and 18 of 75 (24%) of the control group discontinued intervention because of death, major organ failure, adverse events, or non-

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adherence. Furthermore, the study allowed crossover after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors report that the use of unspecified concomitant medications or other supportive care measures were allowed at the discretion of the investigators, adding further uncertainty to the results.

An open-label, randomized, controlled phase II trial (ASSIST) assessed the safety and efficacy of autologous non-myeloablative HCT compared with the standard of care for systemic sclerosis.[39] A small group of consecutively enrolled patients (n=19), all younger than 60 years of age, with diffuse systemic sclerosis were randomly allocated by use of a computer-generated sequence to receive HCT, 200 mg/kg intravenous cyclophosphamide, and rabbit antithymocyte globulin or to 1.0 g/m2 intravenous cyclophosphamide once per month for six months. The primary outcome was improvement at 12 months' follow-up, defined as a decrease in mRSS (<25% for those with initial mRSS >14) or an increase in forced vital capacity by more than 10%. Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. No deaths occurred in either group during follow-up. Patients allocated to HCT (n=10) improved at or before 12 months' follow-up, compared with none of the nine allocated to cyclophosphamide (p=0.00001). Treatment failure (i.e., disease progression without interval improvement), occurred in eight of nine controls compared with none of the 10 patients treated by HCT (p=0.0001). After long-term follow-up (mean 2.6 years) of patients who were allocated to HCT, all but two patients had sustained improvement in mRSS and forced vital capacity, with a longest follow-up of 60 months. Seven patients allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HCT without complication, and all improved after HCT. Four of these patients followed for at least one year had a mean decrease in mRSS points from 27 (standard deviation [SD] 15.5) to 15 (SD 7.4), an increase in forced vital capacity from 65% (SD 20.6) to 76% (SD 26.5) and an increase in total lung capacity from 81% (SD 14.0) to 88% (SD 13.9%). Data for 11 patients with follow-up to two years after HCT suggested that the improvements in mRSS (p<0.0001) and forced vital capacity (p<0.03) persisted.

Nonrandomized Studies

Several nonrandomized studies evaluate stem cell transplantation as summarized below. However, lack of a comparison group limits the ability to identify the treatment effect experienced by these groups of patients over and beyond that experienced by patients undergoing standard care for systemic sclerosis.

Henes (2020) reported results of a prospective non-interventional study of autologous stem cell transplantation for progressive systemic sclerosis from the EBMT Autoimmune Disease Working Party.[40] The primary endpoint was progression-free survival and secondary endpoints were overall survival, non-relapse mortality, response, and incidence of progression. A total of 80 patients were enrolled. Median follow-up was 24 months. Two-year progression-free survival was 81.8%. Two-year outcomes for overall survival, response, and incidence of progression were 90%, 88.7%, and 11.9%, respectively.

Nakamura (2018) evaluated HCT for systemic sclerosis in 14 patients diagnosed within three years prior to enrolling.[41] Median follow-up was 137 months. At 10 years, overall survival was 93% and event-free survival was 40%. Additional immunosuppressive treatments were required in 43% of patients and HCT-related adverse events occurred in 43% of patients as

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well. One patient died of severe cardiomyopathy.

Vonk (2008) reported the results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HCT from 1998 to 2004.[42] There was one transplant-related death and one death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1 to 7.5), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Estimated survival at five years was 96.2% (95% confidence interval [CI]: 89 to 100%) and 84.8% (95% CI: 70.2 to 100%) at seven years. Event-free survival was 64.3% (95% CI: 47.9 to 86%) at five years and 57.1% (95% CI: 39.3 to 83%) at seven years.

Nash (2007) reported the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HCT.[43] Overall and progression-free survival both 64% at five years, respectively.

Henes (2012) reported on their experience with autologous HCT for systemic sclerosis in 26 consecutive patients scheduled for HCT between 1997 and 2009.[44] The major outcome variable was the response to treatment (reduction of modified Rodnan skin score [mRSS] by 25%) at six months. Secondary endpoints were transplant-related mortality and PFS. At six months, significant skin and lung function improvement of the mRSS was achieved in 78.3% of patients. The overall response rate was 91%, as some patients improved after month 6. Three patients died between mobilization and conditioning treatment, two due to severe disease progression and one whose death was considered treatment-related. Seven patients experienced a relapse during the 4.4 years of follow up. PFS was 74%. Four patients died during follow-up, and the most frequent causes of death were pulmonary and cardiac complications of systemic sclerosis. The authors concluded that autologous HCT resulted in significant improvement in most patients with systemic sclerosis.

JUVENILE ARTHRITIS

Silva (2018) reported on 16 patients with juvenile arthritis refractory to standard therapy or who had failed autologous HCT, who underwent allogeneic HCT.[45] Patients experienced significant improvements in arthritis and quality of life, with 11 children achieving drug-free remission at last followup. At median followup of 29 months, one patient died of probable sepsis following an elective surgery and one died of invasive fungal infection, for a treatment-related mortality rate of 12.5%.

A review article by Saccardi (2008) summarized the experience thus far with juvenile idiopathic and rheumatoid arthritis.[46] More than 50 patients with juvenile idiopathic arthritis have been reported to the EBMT Registry. The largest cohort study initially used one conditioning regimen, and thereafter, a modified protocol. Overall drug-free remission rate was approximately 50%. Some late relapses have been reported, and only partial correction of growth impairment has been seen. A new retrospective analysis is ongoing on behalf of the Autoimmune Diseases, Pediatric and Inborn Error EBMT Working Parties. The frequency of HCT for rheumatoid arthritis has decreased significantly since 2000, due to the introduction of new biologic therapies. Most patients who have undergone HCT have had persistence or relapse of disease activity within six months of transplant.

TYPE 1 DIABETES

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Systematic Reviews

Gan (2018) published a meta-analysis of the efficacy of stem cell transplantation in patients with type 1 diabetes.[47] The literature search, conducted through January 2018 identified 22 studies that met inclusion criteria. Among these were nine RCTs with a control group and were double blinded. Eight of the nine were considered to be high quality. Studies were rated for quality using the Jadad scale. A pooled analysis was conducted using a random-effects model and the Begg's funnel plot. Additional subgroup analyses were performed. There was no evidence of significant publication bias. A meta-analysis of the RCTs indicated that HCT treatment increased C-peptide levels and reduced the glycated hemoglobin level compared with the control group. Two RCTs reported fasting plasma glucose at the 12-month follow-up. The pooled effect indicated a reduction in the HCT group (p=0.004) but not in the control group (p=0.323).

El-Badawy and El-Badri (2016) published a meta-analysis on the use of HCT to treat diabetes.[48] The literature search, conducted through August 2015, identified 22 studies for inclusion; study design of included studies was not consistently reported. Fifteen of the studies (n=300 patients) involved patients with type 1 diabetes; 7 studies (n=224 patients) involved patients with type 2 diabetes. The quality of the selected studies was assessed using Cochrane criteria. The following items were evaluated to determine the risk of bias: attrition, confounding measurement, intervention, performance, selection, and conflict of interest.; however, results of the risk of bias assessment were not reported in the publication. The mean follow-up in the studies ranged from 6 to 48 months (median, 12 months). Comparisons of C-peptide levels (C-peptide measures islet cell mass, and an increase after HCT indicates preservation of islet cells) and hemoglobin A1c levels after 12-month follow-up were calculated by type of diabetes (1 or 2) and source of stem cells. Adverse events were reported in 22% of the patients, with no reported mortality. Reviewers concluded that remission of diabetes is possible and safe with stem-cell therapy, patients with previously diagnosed ketoacidosis are not good candidates for HCT, and that early-stage patients may benefit more from HCT. Large-scale well-designed randomized studies considering stem-cell type, cell number, and infusion method are needed.

Nonrandomized studies

Several nonrandomized studies were identified evaluating autologous HCT in patients with new-onset type 1 diabetes. In the series, although a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high.

Gan (2018) evaluated the safety and clinical efficacy of autologous HCT in adolescent patients with newly-diagnosed type 1 diabetes.[47] Of the 40 patients included, 20 received HCT and 20 were treated with insulin injections only. Fourteen of the HCT-treated patients and one insulin-treated patient were insulin-independent for 1.5 to 48 months. Of the 14 insulin-independent HCT patients, 11 relapsed (median time of 19.5 months. At the four-year follow-up, the daily insulin dosages were 0.49 IU/kg/day in the HCT and 0.79 IU/kg/day in the insulin-only group.

Walicka (2018) assessed metabolic control in patients with newly diagnosed type 1 diabetes mellitus following HCT treatment.[49] The study included a total of 23 patients who received HCT and eight control patients. At six months post-transplantation, 22 of 23 transplant patients were insulin-free. At six years post-transplantation, only one transplant patient was insulin-free. Fasting plasma glucose was significantly higher in the control group than the transplanted

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patients at 36 months following transplant, but good glycemic control was reported throughout the observation period.

Cantu-Rodriguez (2016) published a study of 16 patients with type 1 diabetes who received a less toxic conditioning regimen and transplantation.[50] The outpatient procedures were completed without severe complications. At the six-month follow-up, 3 (19%) were nonresponders, 6 (37%) partially independent from insulin, and 7 (44%) were completely independent of insulin. Hemoglobin A1c levels decreased by a mean of -2.3% in the insulin-independent group.

In 2015, Xiang published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than six weeks before study enrollment.[51] After a mean follow-up of 28.5 months (range, 15-38 months), 71 patients (55%) were considered to be insulin-free. These patients had a mean remission period of 14.2 months (SD=6.1 months). The other 57 patients (45%) were insulin-dependent. The latter group includes 27 patients with no response to treatment and another 30 patients who relapsed after a transient remission period. Adverse events included ketoacidosis and renal dysfunction (one patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HCT were younger age at onset of diabetes, lower tumor necrosis factor α, and higher fasting C peptide.

A case series by Snarski (2015) reported on 24 patients with a diagnosis of type 1 diabetes within six weeks of enrollment who underwent autologous HCT.[52] Patients had a mean age of 26.5 years (range, 18-34 years). After treatment, 20 of 23 patients (87%) went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. Median time of remission was 31 months (range, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at two and three years, but the insulin doses returned to pre-HCT levels at years four and 5. Among patients (n=20) remaining in follow-up at the time of data analysis for publication, four (20%) remained insulin-free. Adverse events include neutropenic fever in 12 patients (50%). There were four cases of sepsis, including a fatal case of Pseudomonas aeruginosa sepsis. There was also one case of pulmonary emphysema after insertion of a central venous catheter.

Couri (2009) reported the results of a prospective Phase I/II study of autologous HCT in 23 patients with type 1 diabetes (age range, 13 to 31 years) diagnosed in the previous six weeks by clinical findings with hyperglycemia.[53] After a mean follow-up of just over two years (29.8 months; range, 7-58 months) post-transplantation, the majority of patients achieved insulin independence with good glycemic control. There was no transplant-related mortality. Nevertheless, interpretation of these results is limited by lack of long-term follow-up of primary health outcomes (morbidity and mortality related to diabetes). Additionally, lack of a comparison group limits the possibility of ruling out chance as an explanatory factor.

CROHN DISEASE

Brierley (2018) published a review of patients in the European Society for Blood and Marrow Transplantation registry undergoing autologous HCT for Crohn disease (n=82) who had failed a median of six lines of drug therapy.[54] At median followup of 41 months, 68% achieved either complete remission or significant improvement in symptoms. One patient died of causes relating to the transplant (cytomegalovirus infection, sepsis, and organ failure). At a median of 10 months followup, 73% resumed medical therapy for Crohn disease.

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Hawkey (2015) has conducted the only RCT (ASTIC trial) evaluating the effect of HCT on Crohn disease.[55] Patients were randomized to receive either immunoablation and HCT (n=23) or control (HCT deferred for one year, n=22). The primary endpoint was remission defined as: Crohn Disease Activity Index <150; no use of corticosteroids or immunosuppressive drugs or biologics for three months; and no endoscopic or radiologic evidence of active disease. At one-year followup, two patients in the treatment group and one patient in the control group achieved remission (p=0.6). There were 76 adverse events were reported in patients receiving HCT and 38 in controls. One HCT patient died.

Lindsay (2017) reported additional analyses on the ASTIC trial participants, combining the treatment patients and the control patients who underwent deferred HCT.[56] Outcomes were three-month steroid-free clinical remission at one year and degree of endoscopic healing at one year. Three-month steroid free clinical remission was achieved by 13 of 34 (38%; 95% CI, 22% to 55%) patients who had data available. Complete endoscopic healing was seen in 19 of 38 patients (50%; 95% CI, 34% to 66%). However, serious adverse events (76) were experienced in 23 of 40 patients.

Jauregui-Amezaga (2015) evaluated the safety of HCT for the treatment of refractory Crohn's disease in a prospective study that included 26 patients.[57] The study found very high rates of febrile neutropenia (62% during mobilization and 95% during conditioning). In addition, 12 (57%) patients developed mucositis and two patients experienced hemorrhage.

OTHER AUTOIMMUNE DISEASES

Vanikar (2012) reported the results of a small prospective study (n=11) on the use of allogeneic HCT for treatment of Pemphigus vulgaris (PV).[58] However, patient selection criteria, length of follow-up, and overall survival (or other primary health outcomes) were not stated. Therefore, interpretation of the treatment benefit reported in the manuscript is unclear.

Burt (2019) evaluated HCT for the treatment neuromyelitis optica spectrum disorder in a prospective open-label cohort study.[59] Thirteen patients were enrolled, of which 11 were aquaporin-4-immunoglobulin G [AQP4-IgG]-positive, one was negative, and one was AQP4-IgG-positive with neuropsychiatric systemic lupus erythematosus. Patients were treated with autologous nonmyeloablative hematopoietic stem cell transplantation. The patient with systemic lupus erythematosus died 10 months post-HCT of complications of active lupus. At a median of 57 months of follow-up, 80% of patients were relapse-free off all immunosuppression (p<0.001).

Greco (2015) evaluated HCT for the treatment of refractory neuromyelitis optica in a retrospective study (n=16) using registry data.[60] After a median follow-up period of 47 months, 3/16 (~19%) patients had progression-free disease and were also no longer receiving treatment, indicating that majority of patients continued to progress or relapse over the long term.

No other prospective clinical trials of sufficient size were identified for the use of HCT in other autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others).

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

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In 2018, the American Society for Blood and Marrow Transplantation (ASBMT) published an evidence-based position statement on systemic sclerosis as an indication for autologous hematopoietic cell transplantation.[61] Based on the results of three RCTs and follow-up meta-analyses, they rate the evidence as high-quality and recommend systemic sclerosis as a "standard of care" indication for autologous HCT.

In 2019, the ASBMT published an evidence-based position statement on autologous hematopoietic cell transplantation for treatment-refractory relapsing multiple sclerosis.[62] Based on a review of eight retrospective studies, eight clinical trials, and three meta analyses/systematic reviews, the ASBMT recommends considering treatment-refractory relapsing MS with high risk of future disability a "standard of care, clinical evidence available" indication for autologous HCT.

SUMMARY

There is enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in some patients with systemic sclerosis/scleroderma. In addition, clinical guidelines based on evidence recommend HCT for treatment of systemic sclerosis. Therefore, HCT may be considered medically necessary for treatment of systemic sclerosis/scleroderma when criteria are met.

There is not enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in patients with systemic sclerosis/scleroderma when criteria are not met. Therefore, HCT is considered investigational for treatment of systemic sclerosis/scleroderma when criteria are not met.

There is not enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in patients with other autoimmune diseases. Therefore, autologous or allogeneic HCT is considered investigational for treatment of autoimmune diseases except systemic sclerosis/scleroderma.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

October 1, 2020

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.33

Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma

Effective: December 1, 2019

Next Review: August 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic cell transplant may be considered **medically necessary** in the treatment of central nervous system (CNS) for either of the following (A. or B.):
   A. As a consolidation therapy for previously untreated embryonal tumors of the CNS that show either (1. or 2.):
      1. Partial or complete response to induction chemotherapy, or
      2. Stable disease after induction chemotherapy
   B. As a treatment for recurrent CNS embryonal tumors

II. Hemopoietic cell transplantation is considered **investigational** for any of the following:
   A. Tandem autologous hemopoietic cell transplantation to treat embryonal tumors of the CNS
   B. Allogeneic hemopoietic cell transplantation to treat embryonal tumors of the CNS

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C. Autologous hemopoietic cell transplantation to treat ependymoma

D. Tandem autologous hemopoietic cell transplantation to treat ependymoma

E. Allogeneic hemopoietic cell transplantation to treat ependymoma

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- Documentation of response to induction chemotherapy

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
4. Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas, Transplant, Policy No. 45.34
5. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and

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allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

HEMATOPOIETIC CELL TRANSPLANTATION FOR BRAIN TUMORS

Autologous HCT allows for escalation of chemotherapy doses above those limited by myeloablation and has been tried in patients with high-risk brain tumors in an attempt to eradicate residual tumor cells and improve cure rates. The use of allogeneic HCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction, but rather on a graft-versus-tumor effect. Allogeneic HCT is uncommonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

CNS Embryonal Tumors

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system (CNS) embryonal tumors are more common in children and are the most common brain tumor in childhood. They are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term "primitive neuroectodermal tumor" (PNET), however, histologically similar tumors in different locations in the brain demonstrate different molecular genetic alterations.

Embryonal tumors of the CNS include the following:

- medulloblastoma
- medulloepithelioma
- supratentorial PNETs (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma)
- ependymoblastoma
- atypical teratoid/rhabdoid tumor (AT/RT)

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison. Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiation therapy, as medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification, as average or high risk. The average-risk group includes children older than 3 years, without metastatic disease, and with tumors that are totally or near totally resected (<1.5 cm^2 of residual disease). The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (>1.5 cm^2 of residual disease).[1]

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in 5-year overall survival (OS) rates of 80% or better.[1] For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the

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average event-free survival at 5 years ranges from 34%–40% across studies.[2] Fewer than 55% of children with high-risk disease survive longer than 5 years. The treatment of newly diagnosed (i.e., previously untreated) medulloblastoma continues to evolve, and in children under the age of 3, because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and sometimes avoid the use of radiation, and have included trials of higher-dose chemotherapeutic regimens with autologous HCT.

Supratentorial PNETs (sPNET) are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies.[2] After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to five-year OS rates of 40%–50% have been reported, and for patients with disseminated disease, survival rates at five years range from 10%–30%.[3]

Recurrent childhood CNS embryonal tumor is not uncommon, and depending on which type of treatment the patient initially received, autologous HCT may be an option. For patients who receive high-dose chemotherapy and autologous HCT for recurrent embryonal tumors, objective response is 50%–75%; however, long-term disease control is obtained in fewer than 30% of patients, and is seen primarily in patients in first relapse with localized disease at the time of relapse.[3]

Ependymoma

Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. In children, the tumor typically arises intracranially, while in adults, a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation. Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy usually does not play a role in the initial treatment of ependymoma. However, disease relapse is common, typically occurring at the site of origin. Treatment of recurrence is problematic; further surgical resection or radiation therapy is usually not possible. Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy with autologous HCT has been investigated as a possible salvage therapy.

Note:

- Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. However, these tumors arise from glial cells and not neuroepithelial cells. These tumors are considered in a separate medical policy. See Cross References.
- Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing's sarcoma may be considered PNETs. However, these peripheral tumors are considered in a separate medical policy. See Cross References.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the

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duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. The risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of central nervous system (CNS) embryonal tumors and ependymoma, comparative clinical trials that compare this therapy to standard medical treatment are needed. Further, for treatment of hematologic malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

CNS EMBRYONAL TUMORS

Autologous Transplant for Newly Diagnosed Tumors

Systematic Reviews

In 2013, an updated Cochrane Review analyzed randomized controlled trials (RCTs) comparing high-dose chemotherapy with HCT (i.e. myeloablative therapy) with conventional chemotherapy or no further treatment in children with high-risk neuroblastoma.[4] Three RCTs[5-7] with a total of 739 children were included. There was a statistically significant difference in event-free survival (EFS) and OS in favor of the myeloablative therapy group ($p<0.0006$ and 0.04, respectively). However, analysis of outcomes from the individual studies as well as additional follow-up data from the Matthay trial found no statistically significant between-group difference in OS ($p=0.06$). No significant between group difference was found for treatment-related death, serious infection, or secondary malignant disease. The myeloablative group has significantly higher incidence of renal effects, interstitial pneumonitis, and veno-occlusive disease. The authors concluded that myeloablative therapy appeared to be effective for EFS, but that there was no current evidence of effect on OS when additional follow-up data were included in the analysis.

Randomized Controlled Trials (RCTs)

No new RCTs have been published since the 2013 Cochrane Review.

Nonrandomized Studies

Alsultan (2015) retrospectively reviewed outcomes for 10 children under age 3 years treated with HCT, with or without craniospinal irradiation, for CNS embryonal tumors.[8] Of the 10 patients, five had medulloblastoma, three had AT/RT, one had an embryonal tumor with abundant neuropil and true rosettes, and one had pineoblastoma; all underwent subtotal resection and induction chemotherapy. Five patients received radiotherapy, along with the AT/RT patient, who received radiotherapy as salvage therapy. The PFS was 50% (95% confidence interval [CI], 18% to 75%) at one year and at two years, with a median follow-up of 24 months. All patients with medulloblastoma were alive and without evidence of disease at last follow up, including two with metastatic medulloblastoma who did not receive craniospinal irradiation.

Lester (2014) conducted a retrospective review of 26 patients (11 children and 15 adults) with CNS PNET to evaluate clinical outcomes and prognostic factors.[9] Overall, five-year disease-free survival (DFS) was 78% for pediatric patients and 22% for adult patients ($P=0.004$). Four-year OS was 67% for pediatric patients and 33% for adult patients ($P=0.07$). More pediatric patients were treated with high-dose chemotherapy with stem cell transplant than adult

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patients (82% vs 27%). In unadjusted analysis, compared with standard chemotherapy, treatment with high dose chemotherapy with stem cell transplant was associated with improved OS (HR 0.3; 95% CI 0.1 to 1.0; P=0.05).

Bergthold (2014) reported outcomes for 19 young (age <5 years) children with classical or incompletely-resected medulloblastoma treated with high-dose busulfan-thiotepa with autologous cell transplant, followed by posterior fossa irradiation.[10] Subjects were treated at a single center from 1994 to 2010. On pathology, 14 patients had classic medulloblastoma, while 3 had desmoplastic/nodular medulloblastoma and 1 had medulloblastoma with extensive nodularity. The median follow-up was 40.5 months (range, 14.5–191.2 months). At three and five years, EFS and OS were 68% (95% CI 45 to 84%) and 84% (95% CI 61 to 94%), respectively. Treatment failures occurred in six children at a median time of 13 months (range, 5.8–30.7 months) after HCT. The authors conclude that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

Massimino (2013) reported outcomes for 28 consecutive patients with non-cerebellar PNET treated from 2000 to 2011 with a high-dose drug schedule (methotrexate, etoposide, cyclophosphamide, and carboplatin with or without vincristine) with autologous stem cell rescue, followed by one of two radiation treatment options.[11] For the first 15 patients, high-dose chemotherapy and stem cell rescue was followed by hyperfractionated accelerated craniospinal irradiation (CSI) with two high-dose thiotepa courses following CSI. For subsequent cases, CSI was replaced with focal radiotherapy for patients whose tumors were non-metastatic and not progressing during induction chemotherapy. Three- and 5-year progression-free survival (PFS) rates were 69 ± 9% and 62 ± 10%, respectively; 3- and 5-year event-free survival (EFS) rates were 59±10% and 53±10%, respectively; and 3- and 5-year OS rates were 73±9% and 52± 11%, respectively. Eleven children died at a median of 32 months after their diagnosis (range 5–49 months), eight due to their tumor, one due to multiorgan failure after the first myeloablative treatment, and two due to acute myeloid leukemia and myelodysplastic syndrome which developed 23 and 34 months after their primary diagnosis. For the 25 patients who were able to tolerate the entire schedule, including at least one myeloablative course, the 5-year PFS and OS rates were 67±11% and 61±11%, respectively. Five-year PFS did not differ for patients with pineal tumors versus those with non-pineal tumors (five-year PFS 83±15% vs 54±12%, respectively; P=nonsignificant).

Lee (2012) retrospectively reviewed the medical records of 13 patients diagnosed with atypical teratoid/rhabdoid tumor (AT/RT) who were treated at their institute at Seoul National Children's University Hospital (Korea).[12] The median age was 12 months (range: 3–67 months), and seven patients were younger than one-year old at the time of diagnosis. Three patients (23%) underwent high-dose chemotherapy and autologous HCT. The authors assessed the impact on OS in these three patients, as compared to the remaining 10 patients undergoing other chemotherapy regimens. No statistical difference in OS was observed between these two groups (p=0.36); however, the median survival was reported to be higher in the HCT group (15 months) compared to the non-HCT group (9 months).

Chintagumpala (2009) reviewed event-free survival (EFS) of 16 patients with newly diagnosed (i.e., previously untreated) supratentorial primitive neuroectodermal tumor (sPNET) treated with risk-adapted craniospinal irradiation and subsequent high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) between 1996 and 2003.[13] Eight patients were considered at average risk and 8 were at high risk (defined as the presence of residual tumor larger than 1.5 cm^2 or disseminated disease in the neuroaxis). Median age at diagnosis

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was 7.9 years (range: 3–21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and overall survival (OS) for the patients with average risk disease was 75% (+/- 17%) and 88% (+/- 13%), respectively. For the high-risk patients, these outcomes were 60% (+/- 19%) and 58% (+/- 19%), respectively. No treatment-related toxicity deaths were reported. The authors concluded that high-dose chemotherapy with stem-cell support after risk-adapted craniospinal irradiation allows for a reduction in the dose of radiation needed to treat nonmetastatic, average-risk PNETs, without compromising EFS.

Fangusaro (2008) reported outcomes for 43 children with newly diagnosed (i.e., previously untreated) PNETs treated prospectively on two serial studies (Head Start 1 [HS1] and Head Start 2 [HS2]) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HCT.[2] There were no statistical differences between HS1 and HS2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was partial or complete response, patients underwent myeloablative chemotherapy with autologous HCT (n=32). Patients with progressive disease at the end of induction were not eligible for consolidation. Five-year EFS and OS were 39% (95% CI: 24–53) and 49% [95% confidence interval (CI): 33–62], respectively. Patients with nonpineal tumors did significantly better than patients with pineal PNETs (two-year and five-year EFS of 57% vs. 23% and 48% vs. 15%, respectively and two-year and five-year OS of 70% vs. 31% and 60% vs. 23%, respectively). Sixty percent of survivors were alive without exposure to radiation therapy.

Dhall (2008) reported outcomes for children younger than three years of age at diagnosis of nonmetastatic medulloblastoma, after being treated with five cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HCT.[14] Twenty of 21 children enrolled completed induction chemotherapy, of which 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of seven patients with residual disease at the beginning of induction, all achieved a complete radiographic response to induction chemotherapy. Of the 20 patients who received consolidation chemotherapy, 18 remained free of disease at the end of consolidation. In patients with gross total tumor resection, five-year EFS and OS were 64% (+/- 13) and 79% (+/- 11), respectively, and for patients with residual tumor, 29% (+/- 17) and 57% (+/-19), respectively. There were four treatment-related deaths. The need for craniospinal irradiation was eliminated in 52% of the patients and 71% of survivors avoided irradiation completely, with preservation of quality of life and intellectual functioning.

Gajjar (2006) reported the results of risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and autologous HCT in 134 children with newly diagnosed (i.e., previously untreated) medulloblastoma.[15] After tumor resection, patients were classified as having average-risk disease (n=86), defined as ≤1.5 cm^2 residual tumor and no metastatic disease or high-risk disease (n=48), defined as >1.5 cm^2 residual disease or metastatic disease localized to the neuroaxis. A total of 119 children completed the planned protocol. Five-year OS was 85% (95% CI: 75–94) among the average-risk cases and 70% (95% CI: 54–84) in the high-risk patients. Five-year EFS was 83% (95% CI: 73–93) and 70% (95% CI: 55–85) for average- and high-risk patients, respectively. No treatment-related deaths were reported.

Autologous Transplant for Recurrent Tumors

Systematic Reviews

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In 2013 Kostaras and Easaw published a systematic review of studies of HDCT with HCT for recurrent medulloblastoma in adults included 13 articles[16-25] with a total of 66 adult patients.[26] The analysis found a small population of adult patients for which HDCT with HCT may be a treatment option, including those with recurrent disease confined to the CNS, are unlikely to benefit from conventional chemotherapy, and are otherwise healthy enough to tolerate the treatment. The authors recommended that cases of recurrent adult medulloblastoma in which HCT is being considered should be discussed by a multidisciplinary tumor board including a hematologic oncologist and transplant specialists.

Raghuram (2012) performed a systematic review of the literature regarding the outcome of patients with relapsed sPNET treated with high-dose chemotherapy and autologous HCT.[27] Eleven observational studies published before 2010 met their inclusion criteria; 4 of these were prospective case-series. The 11 studies consisted of 46 patients diagnosed with relapsed sPNET or pineoblastoma who received autologous HCT for treatment of relapse. Of those, 15 patients were children younger than three years of age, and 15 were pineoblastomas. With a median follow-up of 40 months (range 3-123 months) 15 patients were reported alive. Thirteen patients (of 15 survivors) did not receive craniospinal irradiation. The 12-month OS rate of the cohort was 44.2 ± 7.5 months. Twelve-month OS for children younger than 36 months was 66.7 ± 12.2 months, while for older children, 12-month OS was 27.8 ± 10.6 (p=0.003). Twelve-month OS was 20.0 ± 10.3 for those patients with pineoblastoma versus 54.6 ± 9.0 for those with non-pineal sPNETs (p<0.001). Cox regression analysis revealed pineal location as the only independent adverse prognostic factor. Based on these pooled results, high-dose chemotherapy with HCT might lead to survival primarily in younger children with relapsed sPNET, even in the absence of concomitant use of radiotherapy, whereas the outcome in older children and/or in a pineal location is poor with this modality.

Randomized Controlled Trials (RCTs)

No new RCTs have been published since the 2013 Cochrane Review.

Nonrandomized Studies

Egan (2016) reported outcomes from a phase 1 study of temozolomide in combination with thiotepa and carboplatin with autologous HCT in patients with recurrent malignant brain tumors.[28] Temozolomide was administered, followed by thiotepa and carboplatin and then autologous HCT. The study enrolled 27 patients (age range, 3-46 years) with high-grade glioma (n=12), medulloblastoma/PNET (n=9), CNS germ cell tumor (n=4), ependymoma (n=1), and spinal cord PNET (n=1). Fourteen (52%) patients survived longer than 24 months. After 10 years, three patients were alive.

Bode (2014) reported results the intensive-chemotherapy treatment arm of a nonrandomized stratified protocol for the treatment of relapsed cerebral PNET, in which patients could receive intensive chemotherapy, potentially high-dose, or oral chemotherapy.[29] The intensive-chemotherapy arm included 72 patients, 59 who had disseminated disease. Patients received two courses of carboplatin and etoposide; those who had complete or partial remission on MRI received two more cycles of carboplatin and etoposide followed by high-dose chemotherapy with carboplatin, etoposide, and thiotepa, with stem cell rescue. For the cohort of 72 patients, median PFS and OS were 11.6 months (95% CI 10.1 to 13.1 months) and 21.1 months (95% CI 15.7 to 26.5 months) months, respectively. Compared with patients with non-medulloblastoma PNETS, patients with medulloblastoma had longer PFS (12.6 months vs 3.1 months; P=0.004), but not significantly different OS (22.6 months vs 12.3 months; P=0.1).

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Twenty-four patients received high-dose chemotherapy following complete/partial remission on induction therapy, along with 3 patients with stable disease; for those patients, the median PFS and OS were 8.4 months (95% CI 7.7 to 9.1 months) and 20.2 months (95% CI 11.7 to 28.8 months), respectively. Twenty-two patients who had good response to standard chemotherapy and received high-dose chemotherapy with stem cell support were compared with 12 patients who had good response to standard chemotherapy but did not receive subsequent high-dose chemotherapy. Median PFS and OS did not significantly differ between those who did and did not received high-dose chemotherapy.

Allogeneic Transplant

The use of allogeneic HCT for CNS embryonal tumors consists of rare case reports with mixed results.[20,30-32] More data on the use of allogeneic HCT for treatment of these tumors is needed.

Tandem Transplant

In 2016, Sung reported prospective follow-up for 13 children with AT/RT who received tandem HDC and autologous HCT.[33] Five of the children were less than three years old; the remaining eight were three years or older. Tandem HDC and autologous HCT was administered after six cycles of induction chemotherapy with deferred radiotherapy until age three unless the tumor showed relapse or progression in the younger children. Reduced-dose radiotherapy was administered either after two cycles of induction chemotherapy or after surgery with tandem HDC and autologous HCT after six cycles of induction chemotherapy in the older children. All five younger children died from disease progression. Four of the eight older children remained progression-free, with median follow-up of 64 months.

In 2014, Dufour reported outcomes for patients with newly-diagnosed high-risk medulloblastoma and supratentorial PNET treated with tandem high-dose chemotherapy with autologous stem cell support followed by conventional craniospinal radiotherapy.[34] Twenty-four children over the age of 5 were treated from 2001 to 2010, 21 with newly-diagnosed high-risk medulloblastoma (disseminated medulloblastoma or medulloblastoma with residual tumor volume >1.5 cm2 or MYCN amplification) and three with sPNET. Patients received two courses of conventional chemotherapy with carboplatin/etoposide, followed by two courses of high-dose thiotepa followed by stem cell rescue and craniospinal radiotherapy. Twenty-three patients received two courses of high-dose chemotherapy, while one patient received only one course of high-dose thiotepa due to seizures. Median follow up was 4.4 years (range 0.8 to 11.3 years). Three-year EFS and OS were 79% (95% CI 59 to 91%) and 82% (95% CI 62 to 93%), respectively, while five-year EFS and OS were 65% (95% CI 45 to 81%) and 74% (95% CI 51 to 89%), respectively.

Park (2012) reported the results of tandem double high-dose chemotherapy with autologous HCT in six children younger than three years of age with newly diagnosed AT/RT.[35] No treatment-related death occurred during the tandem procedure, and five of six patients were alive at a median follow-up of 13 months (range 7-64) from first HCT. Although three patients remained progression-free after tandem HCT, the effectiveness of this modality is unclear, because all survivors received radiotherapy, as well as tandem HCT.

Sung (2007) reported the results of a single or tandem double high-dose chemotherapy with autologous HCT in 25 children with newly diagnosed (i.e., previously untreated) high-risk or relapsed medulloblastoma or PNET following surgical resection.[36] Three-year EFS for

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patients in complete remission (CR) or partial remission (PR) and less than PR at first high-dose chemotherapy was 67% or 16.7%, respectively. For 19 cases in CR or PR at first high-dose chemotherapy, three-year EFS was 89% in the tandem double group and 44% in the single high-dose chemotherapy group, respectively. Four treatment-related deaths occurred, and in four of eight young children craniospinal radiotherapy was successfully withheld without relapse.

In 2013 Sung reported on 20 consecutive children with high-risk medulloblastoma who received two cycles of chemotherapy combined with radiotherapy and four cycles of post-RT chemotherapy followed by tandem high-dose chemotherapy (HDCT) with autologous SCT.[37] It is unclear whether these patients overlap with the prior study. The tumor relapsed/progressed in four patients, and there were two treatment-related deaths during the second HDCT/autoSCT. Therefore, 14 patients remained event-free at a median follow-up of 46 months (range, 23-82) from diagnosis. The probability of five-year event-free survival was 70.0% ± 10.3% for all patients and 70.6% ± 11.1% for patients with metastases. Late adverse effects evaluated at a median of 36 months (range, 12-68) after tandem HDCT/autoSCT were acceptable.

Sung (2013) also reported on 50 consecutive patients with high-risk neuroblastoma who received tandem HDCT with autologous SCT.[38] Of the 50 patients, 49 underwent a first HDCT/auto-SCT and 47 underwent a second HDCT/auto-SCT. The tumor relapsed or progressed in 14 patients who had either tumor relapse or progression; one patient developed secondary malignancy, one patient died from chronic lung disease, and 34 patients remained event free with a median follow-up of 54.5 months (range, 14-94 months) from diagnosis. Five-year probabilities of OS and EFS were 77% and 71.4%, respectively. However, all patients remained event free for three years or more after tandem HDCT/auto-SCT experienced late adverse effects. The authors concluded that, while outcomes were encouraging for survival, further studies are needed with newer treatment modalities to reduce late adverse effects.

Another study (2010) of tandem high dose chemotherapy with HCT included 19 patients, 12 of which had CNS embryonal tumors.[39] The initial regimen consisted of three days each of carboplatin, etoposide, and thiotepa. Patients without disease progression or excessive toxicity (n=11) received a second regimen of melphalan for three days and cyclophosphamide for four days. Projected overall survival for the 19 patients was 37% and 28% at one and five years, respectively. However, toxicity was significant, including six treatment related deaths. The authors concluded that this regimen was not feasible due to toxicity.

A feasibility study (2012) reported the outcomes of tandem HDC with stem cell rescue (HDC/SCR) for high risk neuroblastoma.[40] Of the 33 patients enrolled, 22 completed one HDC/SCR and 17 patients completed both rounds. There was one transplant-related death. Five-year PFS and OS for all 33 patients was 24.2% and 36.4%, respectively. For patients who received at least one transplant, PFS and OS at five years was 36.4% and 45.5%, respectively. These investigators determined that tandem HDC/SCR is feasible and will be designing a phase III study testing the efficacy of this treatment regimen.

In 2013 Friedrich reported the results of double tandem high-dose chemotherapy with autologous HCT in three children younger than four years of age with metastatic sPNET.[41] These patients also received preventive craniospinal radiotherapy; they had residual disease before HCT, but no evidence of disease after transplant (survival ranging from 2 to 10 years).

EPENDYMOMA

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Literature regarding autologous HCT for the treatment of ependymoma consists primarily of small case series.

Sung (2012) reported the results of tandem double high-dose chemotherapy with autologous HCT in five children younger than three years of age with newly diagnosed anaplastic ependymoma.[42] All patients were alive at median follow-up of 45 months (range 31–62) from diagnosis, although tumor progressed at the primary site in one patient. No significant endocrine dysfunction occurred except for hypothyroidism in one patient, and one patient had significant neurologic injury from primary surgical treatment. The results of this very small case series indicate that treatment with tandem HCT is feasible in very young children with anaplastic ependymoma and that this strategy might also be a possible option to improve survival in these patients without unacceptable long-term toxicity. Further studies with larger patient cohorts are needed to confirm these results.

Mason (1998) reported on a case series of 15 patients with recurrent ependymoma.[43] Five patients died of treatment-related toxicities, eight died from progressive disease, and one died of unrelated causes. After 25 months, 1 patient remains alive, but with tumor recurrence. The authors concluded that their high-dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen.[44]

A small series (2007) reported 5-year EFS of 12% (+/- 6%) and OS of 38% (+/- 10%) among 29 children younger than 10 years of age who received autologous HCT following intensive induction chemotherapy to treat newly diagnosed (i.e., previously untreated) ependymoma.[45] Importantly, radiation-free survival was only 8% (+/- 5%) in these cases. The results of these series, although limited in size, further suggest HCT is not superior to other previously reported chemotherapeutic approaches.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

The from NCCN guidelines for Central Nervous System Cancers (v.2.2019) offer the following on the use of HCT in CNS tumors:[46]

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

For adult medulloblastoma and supratentorial PNET, treatment for recurrence and progression high-dose chemotherapy with autologous stem cell rescue may be considered for patients showing no evidence of disease following resection or conventional reinduction chemotherapy.

SUMMARY

CENTRAL NERVOUS SYSTEM EMBRYONAL TUMORS

Newly Diagnosed Tumors

There is enough research to show that autologous hematopoietic cell transplantation (HCT) has a survival benefit (both event-free and overall) when used to treat newly diagnosed (i.e., previously untreated) central nervous system (CNS) embryonal tumors in patients with

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disease that is considered high-risk. In addition, the use of autologous HCT has allowed for a reduction in the dose of radiation needed to treat both average and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival. Therefore, autologous HCT may be considered medically necessary for previously untreated CNS embryonal tumors in patients who have shown a response to induction chemotherapy or have stable disease after induction chemotherapy.

Recurrent Tumors

It appears that autologous hematopoietic cell transplantation (HCT) may improve survival in patients with recurrent central nervous system (CNS) embryonal tumors, and therefore may be considered medically necessary for these patients.

Allogeneic and Tandem HCT

There is not enough research to show whether tandem hematopoietic cell transplantation (HCT) or allogeneic HCT improves overall health outcomes for people with central nervous system (CNS) embryonal tumors, and therefore both treatments are considered investigational for these tumors.

EPENDYMOMAS

There is not enough research to know if or how well hematopoietic cell transplantation (HCT) improves overall health outcomes for people with ependymoma, and therefore HCT is considered investigational for this indication.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Medical Policy Manual Transplant, Policy No. 45.34

Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas

Effective: April 1, 2020

Next Review: January 2021
Last Review: February 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Autologous HCT is considered **investigational** as a treatment of malignant astrocytomas and malignant gliomas, including both glioblastoma multiforme and oligodendroglioma.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
4. Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33
5. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37

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POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease high-dose chemotherapy (with or without radiation) that is active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

PREPARATIVE CONDITIONING FOR HCT

Autologous HCT necessitates myeloablative chemotherapy to eradicate cancerous cells from the blood and bone marrow, thus permitting subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic progenitor cells. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not graft-versus-host disease.

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ASTROCYTOMAS AND GLIOMAS

Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into three grades of malignancy: grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme. Oligodendrogliomas are diffuse neoplasms that are clinically and biologically most closely related to diffuse fibrillary astrocytomas. However, these tumors generally have better prognoses than diffuse astrocytomas, with mean survival times of ten years versus two to three years. In addition, oligodendrogliomas appear to be more chemosensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than two years for most patients.

Treatment of primary brain tumors focuses on surgery, either with curative intent or optimal tumor debulking. Surgery may be followed by radiation therapy and/or chemotherapy. Survival after chemoradiotherapy is largely dependent on the extent of residual tumor after surgical debulking. Therefore, tumors arising in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex, which typically cannot be extensively resected, have a particularly poor outcome. Treatment of children younger than three years is complicated by the long-term effects of radiation therapy on physical and intellectual function. Therefore, in young children, radiation of the central nervous system (CNS) is avoided whenever possible.

Note: Astrocytomas and gliomas arise from the glial cells. Tumors arising from the neuroepithelium constitute a separate category of malignancies that include CNS neuroblastoma, medulloblastoma, ependymoblastomas, and pinealblastomas. Collectively these tumors may be referred to as primitive neuroectodermal tumors (PNETs). Ependymomas also arise from the neuroepithelium but, because of their more mature histologic appearance, are not considered a member of the PNET family.

EVIDENCE SUMMARY

LITERATURE REVIEWS AND SUMMARY OF THE EVIDENCE TO SUPPORT OUR POSITION.

Systematic Reviews

The 1994 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment[1] concluded that the evidence did not demonstrate that autologous hematopoietic cell transplantation (HCT) improved health outcomes of adult patients with high-grade glial tumors of the brain. The 1999 update of this TEC assessment confirmed these conclusions and noted that although there was much research interest in use of autologous HCT for glioblastoma multiforme due to its uniformly poor prognosis, the published literature was relatively scant, consisting primarily of single-institution case series.

Randomized Controlled Trials

No randomized controlled trials of autologous HCT for astrocytoma or glioma were identified.

Nonrandomized Studies

A 2016 phase I study evaluated the use of high-dose chemotherapy in combination with autologous HCT in patients with recurrent malignant brain tumors.[2] This study included 27

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patients, 12 of whom had high-grade glioma. The authors noted prolonged survival with this treatment regimen, but there was no control group for comparison.

In 2006, Abrey published a phase II study of hematopoietic cell transplantation in 39 patients with newly diagnosed oligodendroglioma.[3] The authors reported the median follow-up of surviving patients was 80.5 months, with 78 months progression-free survival. The overall survival median had not been reached, and 18 patients (46%) had relapsed.

A 2008 study by Finlay compared survival outcomes of 27 children (0.4 to 22 years) with recurrent malignant astrocytomas who underwent myeloablative chemotherapy and autologous HSCT with outcomes in a matched historical cohort (n=56) that received standard chemotherapy regimens following tumor recurrence.[4] Among the 27 children who received myeloablative chemotherapy and autologous HSCT, five (18%) succumbed to treatment-related toxicities within about two months of transplantation, 17 (63%) had disease progression, while five survived and were alive a median of 11 years (range: 8 to 13 years) after transplantation. Overall survival rates at four years were 40 +/- 14% for transplant patients versus 7 +/- 4% with conventional chemotherapy (p=0.018, HR=1.9, 95% CI 1.1 to 3.2). These results suggest myeloablative chemotherapy with autologous HSCT can improve long-term survival among children with recurrent malignant astrocytoma. However, lack of a contemporaneous treatment comparison group precludes conclusions as to the relative efficacy of this approach.

Additional reports on small, uncontrolled series of patients with pontine gliomas,[5] recurrent oligodendrogliomas,[6] or those undergoing radiation therapy for high-grade gliomas[7,8] also did not suggest that this treatment improves survival.

PRACTICE GUIDELINE SUMMARY

The National Comprehensive Cancer Network (NCCN) Guidelines on Central Nervous System cancers (v.3.2019) do not list HCT as a treatment option for patients with astrocytomas or gliomas.[9]

SUMMARY

There is not enough research to show that autologous hematopoietic cell transplantation (HCT) improves health outcomes for patients with malignant astrocytomas and gliomas. No clinical guidelines based on research recommend HCT for people with malignant astrocytomas and gliomas. Therefore, autologous HCT is considered investigational for patients with malignant astrocytomas and gliomas.

REFERENCES

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic

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Codes	Number	Description
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Medical Policy Manual Transplant, Policy No. 45.35

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Effective: December 1, 2019

Next Review: September 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic HCT may be considered **medically necessary** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma in patients with markers of poor-risk disease (see Policy Guidelines). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

II. Allogeneic HCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma who do not meet Criteria I. above.

III. Single Autologous HCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma.

IV. Tandem HCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

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POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

STAGING AND PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Two scoring systems are used to determine stage and prognosis of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). As outlined in Table PG1, the Rai and Binet staging systems classify patients into three risk groups with different prognoses and are used to make therapeutic decisions.

Table PG1. Rai and Binet Classification for CLL/SLL

Rai Stage	Risk	Description	Median Survival, y	Binet Stage	Description	Median Survival, y
0	Low	Lymphocytosis	>10	A	≤3 lymphoid areas, normal hemoglobin and platelets	>10
I	Int	Lymphocytosis + lymphadenopathy	7-9	B	≥3 lymphoid areas, normal hemoglobin and platelets	7
II	Int	Lymphocytosis + splenomegaly ± lymphadenopathy	7-9			
III	High	Lymphocytosis + anemia ± lymphadenopathy or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy	1.5-5			

CLL: chronic lymphocytic leukemia; Int: Intermediate; SLL: small lymphocytic lymphoma.

Because prognoses of patients vary within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table PG2, according to availability in clinical centers.

Table PG2. Markers of Poor Prognosis in CLL/SLL

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Community Center	Specialized Center
• Advanced Rai or Binet stage • Male sex • Atypical morphology or CLL/SLL • Peripheral lymphocyte doubling time <12 mo • $CD38^+$ • Elevated β_2-microglobulin level • Diffuse marrow histology • Elevated serum lactate dehydrogenase level • Fludarabine resistance	• IgVh wild type • Expression of ZAP-70 protein • del 11q22-q23 (loss of *ATM* gene) • del 17p13/mutation *TP53* • Trisomy 12 • Elevated serum CD23 • Elevated serum tumor necrosis factor-α • Elevated serum thymidine kinase

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma.

REDUCED-INTENSITY CONDITIONING (RIC) FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Candidates for RIC

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HCT. These include those whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allogeneic HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HCT if a complete remission could be re-induced with chemotherapy.

Donors

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, with whom usually there is sharing of only three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03

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2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23
4. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Policy No. 45.30

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HST. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of *allogeneic* HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ

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damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in blood, bone marrow, lymph nodes, and spleen, while in SLL they are generally confined to lymph nodes. The Revised European-American/WHO Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.[1]

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (e.g., Richter’s transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.[2]

Treatment regimens used for CLL are generally the same as those used for SLL, and outcomes of treatment are comparable for the two diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses with median survivals of 6 to 10 years, while the median survival of high-risk CLL or SLL may be only two years (see Policy Guidelines). Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural history prompted investigation of hematopoietic cell transplantation as a possible curative regimen.

EVIDENCE SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Systematic Reviews

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A 2015 systematic review of autologous HCT as front-line consolidation in CLL included a literature search through November 2014.[3] Four RCTs in adult patients were included in the review. Outcomes included OS, PFS, EFS, and harms (adverse events, treatment-related mortality and secondary malignancies). Four studies met inclusion criteria, with 301 patients randomized to the autologous HCT arm and 299 to the control arm using front-line therapy without HCT as consolidation. Autologous HCT did not result in a statistically significant improvement in OS (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.62 to 1.33) or in PFS (HR=0.70; 95% CI, 0.32 to 1.52). There was a statistically significant improvement in EFS favoring autologous HCT (HR=0.46; 95% CI, 0.26 to 0.83).There was not a higher rate of secondary malignancy or treatment-related mortality associated with autologous HCT.

This policy initially was based on two TEC Assessments, one from 1999 on autologous hematopoietic cell transplantation (autologous HCT) for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)[4,5], and the other from 2002 on allogeneic hematopoietic cell transplantation (allogeneic HCT) to treat CLL or SLL.[5] Both documents indicated that existing data were insufficient to permit scientific conclusions regarding the use of either procedure, limited by inter-study heterogeneity in patient's baseline characteristics, procedural differences, sample size, and short follow-up.

A systematic review of autologous HCT for CLL or SLL included nine studies (tot[al] n=361, of which 292 were transplanted) identified from a search of MEDLINE databases from 1966 to September 2006.[6] Studies were included if they were full-publication English language reports of prospective randomized, non-randomized, or single-arm design. The analysis suggested that while autologous HCT may achieve significant clinical response rates (74%–100%) with relatively low treatment-related mortality (0–9%), molecular remissions are typically short lived, with subsequent relapse. Overall survival ranged from 68% at three years' follow-up to 58% at six years. Secondary myelodysplasia and myelodysplastic syndrome that may progress to frank acute myelogenous leukemia has been reported in 5%–12% of patients in some studies of autologous HCT, which suggests caution in considering this approach, especially given the indolent nature of CLL or SLL. The authors of the review concluded that in the absence of randomized, comparative studies, it is uncertain whether autologous HCT is superior to conventional chemotherapy (or current chemo-immunotherapy) combinations as first-line consolidation treatment in CLL or SLL patients, regardless of disease risk, or as salvage therapy in those with relapsed disease.

Several non-systematic reviews discuss uncertainties with respect to the type of transplant (autologous vs. allogeneic), the intensity of pretransplant conditioning, the optimal timing of transplantation in the disease course, the baseline patient characteristics that best predict likelihood of clinical benefit from transplant, and the long-term risks of adverse outcomes.[7-11]

Randomized Controlled Trials (RCTs)

The conclusions of the systematic review of autologous HCT outlined above are congruent with results of a Phase III randomized trial by Michallet published in 2010 that compared autologous HCT (n=112) or post-induction observation (n=111) for consolidation in patients with CLL who were in complete remission (CR; 59% of total) or very good partial remission (PR; 27% of total) following fludarabine-containing induction therapy.[12] Patient age ranged from 31-65 years, with Binet stage A progressive (14%), B (66%), and C (20%) disease. None were known to have 17p deletion, 45% were known to not carry 17p deletion, but that status was unknown in 54% of all patients. The primary outcome, median event-free survival (EFS),

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was 51 months (range: 40-62 months) in the autograft group, compared to 24 months (range: 17-32 months) in the observed group; the five-year EFS was 42% and 24%, respectively (p<0.001). The relapse rate at five-year follow-up was 54% in the autograft group versus 76% in the observational group (p<0.001); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range: 59-71 months) and 40 months (range: 25-56 months), respectively (p=0.002). Overall survival probability at five-year follow-up was 86% (95% CI: 77-94%) in the autograft arm, versus 84% (95% CI: 75-93%) in the observation arm (p=0.77), with no evidence of a plateau in the curves. There was no significant difference in NRM between groups, 4% in the autologous HCT group and 0% in the observation group (p=0.33). Myelodysplastic syndrome (MDS) was observed at follow-up in three patients receiving an autograft and in one patient in the observational group.

In a 2013 follow-up report of the Michallet trial, the authors presented quality of life (QoL) findings in the two years after randomization.[13] Two secondary analyses were performed to further investigate the impact of HCT and relapse on QoL. In the primary analysis, the authors demonstrate an adverse impact of HCT on QoL which was largest at four months and continued throughout the first year after randomization. Further, a sustained adverse impact of relapse on QoL was observed which worsened over time. Thus, despite better disease control by autologous HCT, the side effects turned the net effect towards inferior QoL in the first year and comparable QoL in the following two years after randomization.

In a subsequent prospective, randomized clinical trial, Sutton (2011) assessed the efficacy of autologous HCT in previously untreated CLL patients.[14] A total of 244 patients (181 males) of median age 56 years (range 31-66 years) had Binet stage B (n=185) or C (n=56) disease. Among enrollees, 237 started planned therapy, six of whom discontinued. All 231 patients underwent induction chemotherapy; 103 (45%) entered complete remission (CR) and were randomly allocated to autologous HCT (n=52) or observation (n=53). The three-year estimated OS rates were 98% (95% CI: 94%, 100%) in the observation arm, and 96% (95% CI: 90%, 100%) in the HCT arm (p=0.73). The estimated HR for death was 1.2 (95% CI: 0.3, 3.8) in the HCT arm relative to the observation arm (p=0.82). During the 36 months after randomization, HCT was associated, on average, with an extra nine months without clinical symptoms or blood signs of CLL progression (32 ± 1 month) compared with observation (23 ± 2 months).

An editorial that accompanied this report, and which also cited the results from the Michallet study (described above) concluded that autologous HCT in CLL may prolong time to progression and event-free survival, but that because OS is not improved, autologous HCT remains investigational for CLL/SLL patients.[15]

Brion (2012) compared the use of autologous HCT versus treatment with the CHOP (cyclophosphamide, hydroxyldaunorubicin, Oncovin, prednisone) chemotherapy regimen among 86 previously untreated patients (ages 18 to 60) with CLL.[16] The primary outcome was progression-free survival, with overall survival measured as a secondary outcome (all on an intent-to-treat basis). Due to the development of new therapeutic options (such that CHOP is no longer considered first-line treatment for CLL), the study was closed to new patients in 2004 (at which point power calculations indicated that an additional 44 patients would have been needed to see treatment differences between the two groups where there were any). Interpretation of results from this study is thus limited by the potential lack of statistical power to find treatment differences.

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One limitation of the studies cited above is that the standard treatment for CLL has evolved since the initiation of these trials, indicating therefore that all patients may have improved survival statistics from those reported here.[15] Nevertheless, it is not clear that this limitation would necessarily bias results in favor of the autologous transplant group.

ALLOGENEIC HCT

Given that autologous HCT based on myeloablative conditioning regimens has not been demonstrated to be a curative treatment of CLL/SLL, alternative modalities have been sought. Allogeneic HCT has been under investigation for the past two decades based on a potent graft-versus-leukemia (GVL) effect expressed as a permanently active cellular immune therapy in the recipient, independent of chemotherapy-related cytotoxicity. Allogeneic HCT may include use of myeloablative or reduced-intensity pretransplant conditioning regimens.

Systematic Reviews

Kharfan-Dabaja (2018) reported the results of a systematic review comparing the efficacy of myeloablative and reduced intensity conditioning (RIC) allogeneic HCT.[17] Studies that enrolled at least 10 patients with CLL receiving allogeneic HCT were included and evaluated for methodological quality. Forty-eight studies met inclusion criteria, none of which were comparative. Results were reported using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. High heterogeneity between studies was found for those reporting on myeloablative allogeneic HCT for event/progression-free survival, OS, non-relapse mortality, and chronic GVHD, but not for CR or acute GVHD. Among prospective studies investigating allogeneic RCT, heterogeneity was low to moderate, whereas among retrospective studies heterogeneity was moderate to high. Results reported for RIC and myeloablative conditioning were OS (60% [95% CI 56 to 65%] and 51% [95% CI 42 to 61%]), event/progression-free survival (46% [95% CI 41 to 52%] and 41% [95% CI 32 to 50%]), CR (66% [95% CI 57 to 74%] and 58% [95% CI 48 to 67%]), non-relapse mortality (23% [95% CI 19 to 27%] and 32% [95% CI 21 to 44%]), grade 2-4 acute GVHD (46% [95% CI 41 to 52%] and 46% [95% CI 40 to 52%]), and chronic GVHD (all grades; 55% [95% CI 46 to 63%] and 59% [95% CI 46 to 71%]) respectively. A limitation of this study is that not all outcomes were extractable from all included studies and for some outcomes very few studies were available.

Nonrandomized Studies

Helbig (2019) reported outcomes of allogeneic HCT in 30 CLL patients.[18] HLA-matched related donor stem cell grafts were received by 23 patients and matched unrelated donors or HLA-mismatched grafts were received by 7 patients. RIC and MAC regimens were similarly distributed, with 24 patients receiving RIC and 5 receiving MAC. Median follow-up for survivors was 6.8 years. Progression-free and overall survival were 56% and 60%, respectively, at three years. For RIC patients, three-year progression-free and overall survival were 64% and 72%, respectively.

In a 2018 retrospective chart review, van Gorkom reported on CLL patients receiving allogeneic HCT from a haploidentical donor.[19] Data from 117 patients from the European Group for Blood and Marrow Transplantation registry were analyzed to determine outcomes following haploidentical allogeneic HCT and the effect of post-transplantation cyclophosphamide. OS was 48% and 38% at two and five years, respectively. Non-relapse mortality occurred in 40% of patients at two years, with most dying from transplantation-related causes. Cumulative incidence of relapse was 22% and 26% at two and five years,

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respectively. No outcomes were significantly different between those who received post-transplantation cyclophosphamide and those that did not. The authors concluded that the results with haploidentical allogeneic HCT are similar to historical data from HCT with HLA-matched donors. Given this, they suggest that haploidentical HCT should be considered in high-risk patients when an HLA-matched donor is not available.

Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allogeneic HCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation.[20-25] The majority of patients in these series were heavily pretreated, with a median three to five courses of prior regimens. Among individual studies, 27%–57% of patients had chemo-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18%–67%) received stem cells from a donor other than an HLA-identical sibling. Reported NRM, associated primarily with graft-versus-host disease (GVHD) and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 years to 5 years. Overall survival rates ranged from 48%–70%, at follow-up that ranged from two to five years. Similar results were reported for progression-free survival, 34%–58% at two to five years' follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HCT in patients with poor-risk CLL (n=90; median age 53 years, range: 27-65 years), defined as having one of the following: refractoriness or early relapse (i.e., less than 12 months) after purine-analog therapy; relapse after autologous HCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated IgVh status and/or usage of the VH3-21 gene).[26] With a median follow-up of 46 months, four-year NRM, EFS, and OS were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

Additional nonrandomized studies[27-31] have since been published, an example of which is the 20-year cohort study reported by Toze in 2012.[32] The researchers reported similar outcomes (OS of 63% at two years and 55% at five years) among a group of 49 consecutive patients treated with allogeneic HCT who were unresponsive to initial disease treatment.

Although randomized controlled trials are lacking, available evidence from nonrandomized trials is sufficient to suggest the possibility of long-term survival with allogeneic HCT among patients with poor prognosis disease.

TANDEM HCT

The literature search failed to identify studies of tandem HCT for CLL/SLL.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES

Guidelines from NCCN offer the following on the use of HCT in CLL/SLL:[2]

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

For CLL/SLL relapsed/refractory therapy in patients without del(17p)/mut TP53, allogeneic HCT may be considered if without significant comorbidities. In those with del(17p)/mut TP53

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who respond to first-line therapy and have a complex karyotype, allogeneic HCT may also be considered.

Following Richter's transformation, for clonally related diffuse large B-cell lymphoma, following chemotherapy, consider allogeneic HCT when chemotherapy sensitive.

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION (ASBMT) RECOMMENDATIONS

In 2016, the ASBMT published evidence based clinical practice recommendations based on majority consensus vote.[33] For standard-risk CLL, the recommendation is to offer an allo-HCT when there is lack of response or evidence of disease progression after B-cell receptor (BCR) inhibitors. For high-risk CLL, the recommendation is for allo-HCT: for patients showing an objective response to BCR inhibitors or to a clinical trial; for patients showing an objective response to BCL-2 inhibitors, or to a clinical after demonstrating refractory disease to prior therapies including BCR inhibitors; for patients who failed to respond or progressed after BCL-2 inhibitors; for patients with documented Richter transformation who demonstrate an objective response to treatment; and for patients with purine-analogue relapsed or refractory disease.

SUMMARY

ALLOGENEIC HCT

Research suggests allogeneic HCT can provide long-term disease control and overall survival in patients with poor-risk disease; therefore, in select patients, when criteria are met, allogeneic HCT may be considered medically necessary in patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL). There is not enough research to show that allogeneic HCT improves outcomes when criteria are not met. Therefore, the use of allogeneic HCT is considered investigational when policy criteria are not met.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Research suggests that autologous hematopoietic cell transplantation (HCT) is feasible in younger patients, but is not curative, particularly in those with poor-risk chronic lymphocytic leukemia (CLL). Research does not suggest improved overall survival, compared with conventional therapy; therefore, the use of autologous HCT in patients with CLL/ small lymphocytic lymphoma (SLL) is considered investigational.

TANDEM HCT

There is no research on tandem HCT for chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL). More research is needed to know the impact of tandem hematopoietic cell transplantation on health outcomes for people with CLL/SLL. Therefore the use of tandem HCT for CLL/SLL is considered investigational.

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34. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma." Policy No. 8.01.15

CODES

Codes	Number	Description
		Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
		;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
		;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
		;red blood cell removal
	38213	;platelet depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
		Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
		Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic

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S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.36

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Effective: May 1, 2020

Next Review: October 2020
Last Review: December 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. In **children**, allogeneic hematopoietic cell transplantation may be considered **medically necessary** to treat any of the following:
   A. Childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse (For definition of high-risk factors, see Policy Guidelines)
   B. Childhood ALL in second or greater remission
   C. Refractory ALL
   D. Relapsing ALL after a prior autologous hematopoietic cell transplantation

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II. Hematopoietic cell transplantation (autologous or allogeneic) is considered **investigational** for pediatric patients who do not meet Criterion I. above.

III. In **adults**, autologous hematopoietic cell transplantation may be considered **medically necessary** to treat adult acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse (for definition of high-risk factors, see Policy Guidelines).

IV. In **adults**, autologous hematopoietic cell transplantation is considered **investigational** for adult patients who do not meet Criterion III., including but not limited to the following:

   A. Adult ALL in second or greater remission

   B. Refractory ALL

V. In **adults**, allogeneic hematopoietic cell transplantation with myeloablative (conventional) conditioning may be considered **medically necessary** to treat adult patients with any of the following:

   A. ALL in first complete remission for any risk level (for definition of risk factors, see Policy Guidelines)

   B. ALL in second or greater remissions

   C. Relapsed or refractory ALL

   D. Relapsing ALL after a prior autologous hematopoietic cell transplantation

VI. In **adults**, allogeneic hematopoietic cell transplantation is considered **investigational** for patients who do not meet Criteria V. above.

VII. Reduced-intensity conditioning for allogeneic hematopoietic cell transplantation may be considered **medically necessary** as a treatment of ALL in patients who meet *both* of the following criteria:

   A. ALL is in complete marrow and extramedullary first or second remission; and

   B. For medical reasons (see Policy Guidelines), when the patient would be unable to tolerate a standard myeloablative conditioning regimen.

VIII. Allogeneic hematopoietic cell transplantation using reduced-intensity conditioning is considered **investigational** for patients who do not meet Criterion VII. above.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.

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- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

RELAPSE RISK PROGNOSTIC FACTORS

Childhood ALL

Adverse prognostic factors in children include the following:

- Age less than 1 year or more than 9 years
- Male gender
- White blood cell count at presentation above 50,000/µL
- Hypodiploidy (<45 chromosomes)
- t(9:22) or BCR/ABL fusion
- t(4;11) or MLL/AF4 fusion, and
- ProB or T-lineage immunophenotype.

Several risk stratification schema exist, but, in general, the following findings help define children at high risk of relapse:

- Poor response to initial therapy including:
    - Poor response to prednisone prophase defined as an absolute blast count of 1,000/µL or greater, or
    - Poor treatment response to induction therapy at 6 weeks with high risk having ≥1% minimal residual disease measured by flow cytometry)
- All children with T-cell phenotype,
    a. Patients with either the t(9;22) or t(4;11) regardless of early response measures.

Adult ALL

Risk factors for relapse are less well defined in adults, but a patient with any of the following may be considered at high risk for relapse:

- Age greater than 35 years,
- Leukocytosis at presentation of >30,000/µL (B-cell lineage) and >100,000/µL (T-cell lineage),
- “Poor prognosis” genetic abnormalities like the Philadelphia chromosome (t(9;22)),
- Extramedullary disease
- Time to attain complete remission longer than 4 weeks
  (American Society of Hematology Education Program Handbook, 2007).

REDUCED-INTENSITY CONDITIONING (RIC)

Some patients for whom a conventional myeloablative allogeneic hematopoietic cell transplantation (HCT) could be curative may be considered candidates for RIC allogeneic HCT. These include those whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low

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Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

Note: Unless otherwise specified in the text of this Policy, it is assumed that the term "allogeneic HCT" refers to the use of a myeloablative pretransplant conditioning regimen.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of graft-versus-host-disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant
- Documentation of Relapse Risk Prognostic Factors
- For patients with a reduced-intensity conditioning (RIC) regimen, documentation supporting reasons patient is unable to tolerate a myeloablative conditioning regimen.

CROSS REFERENCES

1. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
2. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
3. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

BACKGROUND

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONVENTIONAL PREPARATIVE CONDITIONING FOR HEMATOPOIETIC SCT

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

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ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Childhood ALL

ALL is the most common cancer diagnosed in children and represents almost 25% of cancers in children younger than 15 years.[1] Complete remission of disease is now typically achieved with pediatric chemotherapy regimens in approximately 95% of children with ALL, with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large, randomized trials, integration of presymptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment.[2]

ALL is a heterogeneous disease with different genetic alterations resulting in distinct biologic subtypes. Patients are stratified according to certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse.[3] Two of the most important factors predictive of risk are patient age and white blood cell count (WBC) at diagnosis.[2] Certain genetic characteristics of the leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows:[2]

FACTOR	FAVORABLE	UNFAVORABLE
Age at diagnosis	1-9 years	<1 or >9 years
Sex	Female	Male
WBC count	<50,000/µL	≥50,000/µL
Genotype	Hyperdiploidy (>50 chromosomes) t(12;21) or *TEL/AML1* fusion	Hypodiploidy (<45 chromosomes) t(9:22) or *BCR/ABL* fusion t(4;11) or *MLL/AF4* fusion
Immunophenotype	Common, preB	ProB, T-lineage

Adolescents and Young Adults (AYA) ALL

The age range for AYA varies across studies, but was defined by the National Cancer Institute as 15 to 39 years. AYA ALL patients are a unique population and may receive treatment based either on pediatric or adult protocols depending on local institutional practices.[4] Cure rates for AYA ALL are less favorable than childhood ALL with five-year event-free survival (EFS) ranging from 63%-74% for patients treated with pediatric protocols versus 34% to 49% for patients who receive an adult treatment protocol. Differences in the frequency of genetic abnormalities that characterize AYA ALL versus childhood ALL help in part to explain the survival differences between the two groups. For example, the “good prognosis” genetic abnormalities like hyperdiploidy and TEL-AML1 gene fusion expressed from t(12;21) chromosome translocation are seen much less commonly in AYA ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities like ALL with BCR-ABL (the Philadelphia chromosome [Ph-positive or Ph+ ALL]; translocation t[9;22]) is higher in AYA ALL than in childhood ALL.

Adult ALL

ALL accounts for approximately 20% of acute leukemias in adults. Approximately 60%–80% of adults with ALL can be expected to achieve complete remission after induction chemotherapy;

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however, only 35%–40% can be expected to survive 2 years.[5] As with AYA ALL, favorable cytogenetic subtypes such as hyperdiploidy and t(12;21) are seen much less commonly in adult ALL than in childhood ALL while Ph-positive ALL is seen in 25%–30% of adult ALL but infrequently in childhood ALL (3%). Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of >30,000/µL (B-cell lineage) and >100,000/µL (T-cell lineage).

EVIDENCE SUMMARY

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Technology Assessments

The policy on childhood ALL was initially based on BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) Assessments completed in 1987 and 1990.[6,7] In childhood ALL, conventional chemotherapy is associated with complete remission rates of about 95%, with long-term durable remissions of 60%. Therefore, for patients in a first complete remission (CR1), hematopoietic cell transplantation (HCT) therapy is considered necessary only in those with risk factors predictive of relapse (see Policy Guidelines section).

The prognosis after first relapse is related to the length of the original remission. For example, leukemia-free survival is 40%–50% for children whose first remission was longer than three years, compared to only 10%–15% for those with early relapse. Thus, HCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with either autologous or allogeneic HCT are unknown.

Systematic Reviews

A 2012 updated systematic review was sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) and included published literature through mid-October 2010 on HCT in children with ALL.[8] The literature consisted mainly of retrospective reviews and also included three RCTs.[9-11] In addition, most of the studies were conducted prior to the availability of tyrosine kinase inhibitors (TKIs) and newer chemotherapy drugs with improved event-free survival (EFS). Due to the limited evidence, the recommendations were based on consensus and expert opinion.

Randomized Controlled Trials

Three reports describing the results of RCTs that compared outcomes of HCT to outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC Assessment.[12-14] The children enrolled in the RCTs were being treated for high-risk ALL in CR1 or for relapsed ALL. These studies reported that overall outcomes after HCT were generally equivalent to overall outcomes after conventional-dose chemotherapy. While HCT administered in CR1 was associated with fewer relapses than conventional-dose chemotherapy, it was also associated with more frequent deaths in remission (i.e., from treatment-related toxicity).

A more recently published randomized trial (PETHEMA ALL-93, n=106) demonstrated no significant differences in disease-free survival or overall survival rates at median follow-up of 78 months in children with very high-risk ALL in CR1 who received allogeneic or autologous HCT versus standard chemotherapy with maintenance treatment[9]. Similar results were observed using either intention-to-treat (ITT) or per-protocol (PP) analyses. However, the

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authors pointed out several study limitations that could have affected outcomes, including the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HCT and time elapsed between CR and undertaking of assigned treatment; and the use of genetic randomization based on donor availability rather than true randomization for patients included in the allogeneic HCT arm.

Nonrandomized Studies

The bulk of the published data for childhood ALL consists of case series[15-17] and retrospective reviews.[18-24] While the subjects in these studies had some variation in age (i.e., infants, children, adolescents) and risk factors (e.g., Philadelphia chromosome-positive), the outcomes showed promising results for allogeneic HCT in patients in CR1 at high risk for recurrence, following relapse and in patients in second or greater remission.

Section Summary

These results suggest that while overall and event-free survival are not significantly different after HCT compared to conventional-dose chemotherapy, HCT remains a therapeutic option in the management of childhood ALL, especially for patients considered at high risk of relapse or following relapse. This conclusion is further supported by the 2012 ASBMT systematic review summarized above. In addition, some investigators recommend that patients should be selected for this treatment using risk-directed strategies.[17,25]

ADULT ALL

Systematic Reviews

Pidala published a 2011 Cochrane systematic review of randomized controlled trials comparing the effect of matched sibling donor vs. no donor status for adults with ALL in first complete remission (CR1).[26] A total of 14 relevant trials were identified, consisting of a total of 3157 patients. Matched sibling donor allogeneic HCT was superior CR1 therapy in ALL patients aged 15 years or over for overall survival (p=0.01), disease-free survival (p=0.004), and reduced relapse risk (p=0.0004). The authors cautioned that “these data are based on adult ALL treated with largely total body irradiation-based myeloablative conditioning and sibling donor transplantation and, therefore, cannot be generalized to pediatric ALL, alternative donors including HLA (human leukocyte antigen) mismatched or unrelated donors, or reduced toxicity or non-myeloablative conditioning regimens.

A 2012 evidence-based update of previous evidence reviews sponsored by the American Society for Blood and Marrow Transplantation (ASBMT)[27,28] included published literature through mid-October 2010.[29,30] Seven RCTs[31-37] were included in the review. The ASBMT determined that the evidence supported the following grade A (at least one meta-analysis, systematic review, or RCT) conclusions and treatment recommendations:

- Myeloablative allogeneic HCT is an appropriate treatment for adult (<35 years) ALL in first complete remission for all disease risk groups. Allogeneic HCT provided a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph-negative ALL patients compared with less intensive chemotherapy regimens. Higher transplant-related mortality in adults over 35 years of age diminished the significant survival advantage.

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- Reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but data were insufficient to make a recommendation. Therefore, reduced-intensity regimens were determined to be appropriate only in adults with ALL in remission who are unsuited for myeloablative conditioning.
- Allogeneic HCT is recommended over chemotherapy for adults with ALL in second complete remission or greater.
- Allogeneic is superior to autologous HCT, though there are insufficient data to determine if this is more apparent in disease risk subgroups including Ph+ ALL.
- There are similar survival outcomes after related and unrelated allogeneic HCT.
- In the absence of a suitable allogeneic donor, autologous HCT may be an appropriate therapy. Although survival outcomes appear similar between autologous HCT and post-remission chemotherapy, the shorter treatment duration with the former is an advantage, but results in a high relapse rate.
- It is appropriate to consider cord blood transplantation for patients with no HLA well-matched donor or those needing an urgent transplant.
- Imatinib therapy before and/or after HCT for Ph+ ALL yields significantly superior overall and leukemia-free survival outcomes.

A meta-analysis published in 2013 included 13 studies (total N = 2962), several of which are described in this Policy.[38] The results suggest that a matched sibling donor myeloablative HCT improves survival only for younger adults (<35 years old) in CR1 compared to chemotherapy, with an absolute benefit of 10% at five years. The analysis also suggests a trend toward inferior overall survival among autologous HCT recipients compared to chemotherapy in CR1 (OR 1.18; 95% CI, 0.99 to 1.41, p=0.06), primarily due to higher treatment-related mortality (TRM) in the autograft patients compared to chemotherapy recipients. These results indicate further study is needed to determine the optimal therapy for adult ALL patients.

Section Summary

Current data from randomized controlled trials indicate post-remission myeloablative allogeneic HCT is an effective therapeutic option for a large proportion of adults with ALL. However, the increased morbidity and mortality from GVHD limit its use, particularly for older patients. Even for adults who survive the procedure, there is a significant relapse rate. Nevertheless, current evidence supports the use of myeloablative allogeneic HCT for patients with ALL in CR1 whose health status is sufficient to tolerate the procedure (see Policy Guidelines).

REDUCED-INTENSITY CONDITIONING (RIC) ALLOGENEIC HCT

There is a substantial graft-versus-malignancy (GVM) effect of postremission allogeneic SCT. RIC regimens have been investigated as a means to extend this GVM effect to patients who could benefit from this procedure but who are ineligible or would not tolerate a fully myeloablative procedure.

Systematic Review

A systematic review published by Abdul Wahid[39] in 2014 included a meta-analysis of data from five studies in which RIC conditioning (n=528) was compared with myeloablative conditioning regimens (n=2489) in adult patients with ALL who received allogeneic HCT mostly in CR1. This analysis of data from nonrandomized studies suggests progression-free survival

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at one to six years was significantly lower after RIC conditioning (36%) compared with myeloablative conditioning (41%) (OR=0.76; 95% CI, 0.61 to 0.93; p<0.01). However, this was probably offset by the significantly lower non-relapse mortality in the RIC group compared with the myeloablative group (OR=0.76; 95% CI, 0.61 to 0.95), resulting in similar overall survival (OR=1.03; 95% CI, 0.84 to 1.26; p=0.76). The use of RIC also was associated with lower rates of GVHD but higher rates of relapse compared with myeloablative conditioning (OR=1.77; 95% CI, 1.45 to 2.71; p<0.000). Studies included in the review were limited by the small number of studies, inter-study heterogeneity for GVHD data, and publication bias for progression-free survival.

Nonrandomized Studies

Rosko (2017) used Center for International Blood and Marrow Transplant Research registry data to examine the effectiveness of RIC HCT in adults 55 years or older with B-cell ALL and explored prognostic factors associated with long-term outcomes.[40] The authors evaluated 273 participants with B-cell ALL with disease status in CR1 (71%), CR2 or beyond (17%), and primary induction failure/relapse (11%) who underwent RIC HCT between 2001 and 2012. Among patients with available cytogenetic data, 50% were Ph-positive. The three-year OS rate was 38% (95% CI, 33% to 44%). The three-year cumulative incidences of non-relapse mortality and relapse were 25% (95% CI, 20% to 31%) and 47% (95% CI, 41% to 53%), respectively.

In a multicenter single-arm study of patients (n=43, median age 19 years; range: 1–55) in second complete remission (CR2), a three-year OS rate of 30% was achieved, with 100-day and NRM rates of 15% and 21%, respectively. Despite achievement of complete donor chimerism in 100% of the patients, 28 (65%) had leukemic relapse, with 67% ultimately succumbing to their disease.[41]

A registry-based study included 97 adult patients (median age 38 years, range 17–65) who underwent RIC and allogeneic HCT to treat ALL in CR1 (n=28), beyond CR1 (CR2/CR3, n=26/5), and advanced or refractory disease (n=39).[42] With median follow-up of about three years, in the overall population two-year OS was 31%, with non-relapse mortality of 28% and relapse rate of 51%. In patients transplanted in CR1, OS was 52%; in CR2/CR3, it was 27%; in patients with advanced or refractory ALL, OS was 20%. These data suggest RIC and allogeneic HCT have some efficacy as salvage therapy in high-risk ALL.

RIC for allogeneic SCT was investigated in a prospective Phase II study that included 37 consecutive adults (median age 45 years; range 15–63 years) with high-risk ALL (43% Ph-positive, 43% high WBC) in CR1 (81%) or CR2 (19%) who were ineligible to receive a myeloablative allogeneic HCT because of age, organ dysfunction, low Karnofsky performance status (<50%), or the presence of infection.[43] Patients received stem cells from a matched sibling (n=27) or matched unrelated donor (n=10). Postremission RIC conditioning consisted of fludarabine and melphalan, with GVHD prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib prior to HCT. The three-year cumulative incidence of relapse was 19.7% + 6.9%, that of NRM was 17.7% + 6.9%. The three-year cumulative OS rate was 64.1% + 8.6%, with DFS rate of 62.6% + 8.5% at the same point. After a median follow-up of 36 months (range: 121–96 months), 25 (67.6%) of patients remained alive, among whom 24 (96%) remained in continuous CR.

A multicenter prospective study published in 2010 involved 47 pediatric patients (median age 11 years, range: 2-20 years) with hematologic cancers, including ALL (n=17), who underwent

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allogeneic HCT with a fludarabine-based RIC regimen.[44] This study represents the first large cooperative group study to be published in this setting. Among the 17 ALL cases, four were in CR2, 12 in CR3, and one had secondary ALL. All patients were heavily pretreated, including previous myeloablative allogeneic or autologous HCT, but these were not individually reported. While most data were presented in aggregate, some survival findings were specified, showing EFS of 35% and OS of 37% at two-year follow-up for the ALL patients. Although most patients lived only a few months after relapse or rejection, some were long-term survivors after further salvage treatment. Among those, one ALL patient received chemotherapy and donor lymphocyte infusion (DLI) for low chimerism and relapse and was reported alive one year following DLI and three years from HCT. A second ALL case, who rejected an initial mismatched-related donor graft, underwent a second RIC regimen using the same donor and was alive with moderate chronic GVHD more than three years after HCT. Treatment-related mortality was not reported by disease, nor was HCT-related morbidities. However, these data do suggest allogeneic HCT with RIC can be used in children with high-risk ALL and achieve some long-term survival in patients with no therapeutic recourse.

Section Summary

Based on currently available data and clinical input, there is sufficient evidence to conclude that RIC allogeneic HCT may be beneficial in patients who demonstrate complete marrow and extramedullary first or second remission, but who, for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Additional data are necessary to determine whether some patients with ALL and residual disease may benefit from RIC allogeneic HCT.

ALLOGENEIC TRANSPLANT AFTER PRIOR FAILED AUTOLOGOUS TRANSPLANT

A 2000 BCBSA TEC Assessment focused on allogeneic HCT after a prior failed autologous HCT, in the treatment of a variety of malignancies, including ALL.[45] The BCBSA TEC Assessment found that data were inadequate to permit conclusions about outcomes of this treatment strategy. Since the TEC assessment, there continues to be a lack of strong evidence on allogeneic HCT in this circumstance. However, it has gained support in the clinical setting as it is potentially curative and has been shown to be of clinical benefit in other hematologic malignancies.

PRACTICE GUIDELINE SUMMARY

The following U.S. professional associations have published position statements for the diagnosis and treatment of ALL:

THE NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

Guidelines from the National Comprehensive Cancer Network (NCCN) for pediatric (v2.2020) and adult (v2.2019) ALL indicate allogeneic hematopoietic cell transplantation (allo-HCT) is appropriate for consolidation treatment of most poor risk (eg, the Philadelphia chromosome−positive, relapsed, or refractory) patients with ALL.[4,46] The guidelines state that for appropriately fit older adults with ALL who are achieving remission, “consideration of autologous or reduced-intensity allogeneic stem cell transplantation may be appropriate.” Of note, the NCCN guidelines stratify treatment according to the categories adolescent and young adult (age 15-39 years) and adult (age 40 or more years), rather than the more traditional categorization of children (18 years or younger) and adult categories (18 or more years). They

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add that chronologic age is not a good surrogate for fitness for therapy and that patient should be evaluated on an individual basis.

THE AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION (ASBMT)

The 2012 ASBMT systematic reviews and guidelines for adults[30] and children[47] are summarized above.

In 2015, guidelines from the American Society for Blood and Marrow Transplantation were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on the use of HCT in and out of the clinical trial setting. Recommendations on ALL are listed in Table 1.

Table 1. Guidelines for Autologous and Allogeneic HCT Indication

Indication	Children (Age <18 Years)		Adults (Age ≥18 Years)	
	Allogeneic HCT	Autologous HCT	Allogeneic HCT	Autologous HCT
First complete response, standard-risk	N	N	S	C
First complete response, high-risk	S	N	S	N
Second complete response	S	N	S	C
At least third complete response	C	N	C	N
Not in remission	C	N	C	N

C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

SUMMARY

AUTOLOGOUS HCT

Current research suggests that autologous hematopoietic cell transplantation (HCT) may be considered a therapeutic option in the treatment of acute lymphoblastic leukemia (ALL) in select adult patients. Therefore, autologous HCT may be considered medically necessary when criteria are met. However, the evidence is insufficient to permit conclusions about the safety and effectiveness of HCT for ALL patients who do not meet the medical necessity criteria; therefore, HCT is considered investigational for those patients.

ALLOGENEIC HCT WITH MYELOABLATIVE CONDITIONING

Current research indicates myeloablative allogeneic hematopoietic cell transplantation (HCT) is an effective therapeutic option for a large proportion of patients with acute lymphoblastic leukemia (ALL). Therefore, myeloablative allogeneic HCT may be considered medically necessary when criteria are met. However, adverse effects from graft versus host disease (GVHD) can be severe, particularly for older or debilitated patients, and there is a significant relapse rate. Therefore, the use of myeloablative allogeneic HCT is considered investigational for patients with ALL who do not meet the medical necessity criteria.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Current research is sufficient to determine that reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) may be considered medically necessary in patients with acute lymphoblastic leukemia (ALL) in complete first or second remission who, for medical reasons, would be unable to tolerate a conventional myeloablative

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conditioning regimen. Current evidence is insufficient to permit conclusions about the safety and effectiveness of RIC allogeneic HCT for all other ALL patients. Additional studies are necessary to determine which, if any, of these patients are most likely to benefit from this treatment regimen. Therefore, allogeneic HCT using RIC is considered investigational for patients with ALL who do not meet the medical necessity criteria.

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48. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia." Policy No. 8.01.32

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.37

Hematopoietic Cell Transplantation for Solid Tumors of Childhood

Effective: December 1, 2019

Next Review: August 2020
Last Review: October 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Note: This policy addresses only solid tumors of childhood. Solid tumors in adults are considered separately in Transplant, Policy No. 45.27. This policy also does not address hematopoietic cell transplantation (HCT) as a treatment of embryonal tumors arising in the central nervous system (cerebral neuroblastoma), tumors derived from glial cells (i.e., astrocytoma, oligodendroglioma, or glioblastoma multiforme), or germ cell tumors which are considered separately in Transplant, Policy Numbers 45.33, 45.34, and 45.38, respectively.

I. **Autologous** hemopoietic cell transplantation may be considered **medically necessary** for any of the following indications (A.-C.):

   A. Ewing's sarcoma when either of the following are met:

      1. For initial treatment of high-risk Ewing's sarcoma. Patients may be categorized as "high-risk" if any of the following are present: metastatic

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disease, unfavorable tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, or older age of the patient.

2. To consolidate remissions or as a salvage therapy for those with residual, recurrent or refractory Ewing's sarcoma.

B. Neuroblastoma when either of the following are met:

1. For initial treatment of high-risk neuroblastoma. Patients may be characterized as high-risk if any of the following are present: age older than 1 year, disseminated disease, MYCN oncogene amplification, or unfavorable histopathologic findings.

2. Recurrent or refractory neuroblastoma.

C. Wilms tumor, recurrent, high-risk

D. Metastatic retinoblastoma

II. **Tandem autologous** hematopoietic cell transplantation may be considered **medically necessary** for high-risk neuroblastoma characterized by any of the following: age older than 1 year, disseminated disease, MYCN oncogene amplification, or unfavorable histopathologic findings.

III. The following are considered **investigational**:

A. Autologous hemopoietic cell transplantation for the following indications: Initial treatment of low- or intermediate-risk Ewing's sarcoma; initial treatment of low- or intermediate-risk neuroblastoma; other solid tumors of childhood, including but not limited to the following: a) Osteosarcoma, b) Retinoblastoma without metastasis, c) Rhabdomyosarcoma, d) Wilms tumor, other than recurrent, high-risk.

B. Tandem or multiple hematopoietic cell transplantation for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma (criterion II.)

C. Allogeneic (myeloablative or nonmyeloablative) hematopoietic cell transplantation for treatment of all pediatric solid tumors.

D. Salvage allogeneic hematopoietic cell transplantation for all pediatric solid tumors that relapse after autologous transplant or fail to respond.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.

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- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Ewing's Sarcoma, neuroblastoma, or Wilms tumor: Indicate if high-risk
- Ewing's Sarcoma: Indicate if request is to consolidate remissions or as a salvage therapy for those with residual, recurrent or refractory Ewing's sarcoma
- Neuroblastoma: Indicate if request is for recurrent or refractory neuroblastoma
- Tandem autologous hematopoietic cell transplantation for high-risk neuroblastoma, indicate if any of the following are present:
    - age older than 1 year,
    - disseminated disease,
    - MYCN oncogene amplification,
    - or unfavorable histopathologic findings.

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
4. Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33
5. Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas, Transplant, Policy No. 45.34
6. Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION FOR SOLID TUMORS

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

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Although cord blood is an allogeneic source, the cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Autologous HCT takes advantage of the steep dose-response relationship observed with many chemotherapeutic agents and allows for escalation of chemotherapy doses above those limited by myeloablation. The use of allogeneic HCT for solid tumors relies on a graft-versus-tumor effect. Allogeneic HCT is uncommonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

SOLID TUMORS OF CHILDHOOD

Solid tumors of childhood are defined as those not arising from myeloid or lymphoid cells. Some of the most common solid tumors of childhood are neuroblastoma, Ewing’s sarcoma/Ewing’s Sarcoma Family of Tumors, Wilms tumor, rhabdomyosarcoma, osteosarcoma, and retinoblastoma.

The prognosis for pediatric solid tumors has improved over the last two decades, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiation therapy).[1] However, patients with metastatic, refractory, or recurrent disease continue to have poor prognoses, and these “high-risk” patients are candidates for more aggressive therapy, including autologous HCT, in an effort to improve event-free survival (EFS) and overall survival (OS).

Descriptions of the solid tumors of childhood that are addressed in this policy are as follows:

PERIPHERAL NEUROBLASTOMA

Note: Cerebral neuroblastoma is considered separately in Transplant No. 45.33 related to embryonal tumors.

Neuroblastoma is the most common extracranial solid tumor of childhood[2], with 90% of cases presenting in children ages 5 or younger.[3] These tumors originate where sympathetic nervous system tissue is present, within the adrenal medulla or paraspinal sympathetic ganglia. They are remarkable for their broad spectrum of clinical behavior, with some undergoing spontaneous regression, others differentiating into benign tumors, and still others progressing rapidly and resulting in patient death.

Patients with neuroblastoma are stratified into prognostic risk groups (low, intermediate, and high) that determine treatment plans. Risk variables include age at diagnosis, clinical stage of disease, tumor histology, and certain molecular characteristics, including the presence of the MYCN oncogene. Tumor histology is categorized as favorable or unfavorable, according to the degree of tumor differentiation, proportion of tumor stromal component, and index of cellular proliferation.[4] It is well established that MYCN amplification is associated with rapid tumor progression and a poor prognosis[5], even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q occurs frequently in neuroblastoma.[6] Although 1p LOH is associated with MYCN amplification, 11q is usually found in tumors without this abnormality. Some recent studies have shown that 1p LOH and unbalanced 11q LOH are strongly associated with outcome in patients with neuroblastoma, and both are independently predictive of worse progression-free survival (PFS) in patients with low- and intermediate-risk disease. Although the use of these LOH markers in assigning treatment in patients is evolving, they may prove useful to stratify treatment.

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Clinical stage of disease is based on the International Neuroblastoma Staging System (INSS) as follows:

- Stage 1

  Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes negative for tumor.

- Stage 2A

  Localized tumor with incomplete gross excision; lymph nodes negative for tumor.

- Stage 2B

  Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor.

- Stage 3

  Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration or by lymph node involvement.

- Stage 4

  Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S.

- Stage 4S

  Localized primary tumor as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (marrow involvement less than 10%), limited to children younger than 1 year of age.

The low-risk group includes patients younger than 1 year of age with stage 1, 2, or 4S with favorable histopathologic findings and no MYCN oncogene amplification. High-risk neuroblastoma is characterized by an age older than 1 year, disseminated disease, MYCN oncogene amplification, and unfavorable histopathologic findings.

In general, most patients with low-stage disease have excellent outcomes with minimal therapy, and with INSS stage 1 disease, most patients can be treated by surgery alone.[2] Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.[2] In contrast, most children older than 1 year with advanced-stage disease die due to progressive disease, despite intensive multimodality therapy[2], and relapse remains common. Treatment of recurrent disease is determined by the risk group at the time of diagnosis, and the extent of disease and age of the patient at recurrence.

EWING'S SARCOMA AND THE EWING FAMILY OF TUMORS

Ewing's sarcoma family of tumors (ESFT) encompasses a group of tumors that have in common some degree of neuroglial differentiation and a characteristic underlying molecular pathogenesis (chromosomal translocation). The translocation usually involves chromosome 22 and results in fusion of the EWS gene with one of the members of the ETS (E-twenty-

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six) family of transcription factors, either FLI1 (90–95%) or ERG (5–10%). These fusion products function as oncogenic aberrant transcription factors. Detection of these fusions is considered to be specific for the ESFT, and helps further validate the diagnosis. Included in ESFT are “classic” Ewing’s sarcoma of bone, extraosseous Ewing’s, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumors (chest wall).

Most commonly diagnosed in adolescence, ESFT can be found in bone (most commonly) or soft tissue; however, the spectrum of ESFT has also been described in various organ systems. Ewing’s is the second most common primary malignant bone tumor. The most common primary sites are the pelvic bones, the long bones of the lower extremities, and the bones of the chest wall.

Current therapy for Ewing’s sarcoma favors induction chemotherapy, with local control consisting of surgery and/or radiation (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiation therapy have improved the PFS in patients with localized disease to 60%–70%.[7] The presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for patients presenting with metastatic disease is poor, with 20%–30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing’s are tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, or older age of the patient. However, “high-risk” Ewing’s has not always been consistently defined in the literature.

RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma of childhood, shows skeletal muscle differentiation. The most common primary sites are the head and neck (e.g., parameningeal, orbital, pharyngeal), genitourinary tract, and extremities.[8] Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70%–80%.[9] However, approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the five-year survival is 20%–30% for this “high-risk” group.[9,10]

WILMS TUMOR

Wilms tumor, the most common primary malignant renal tumor of childhood, is highly sensitive to chemotherapy and radiation, and current cure rates exceed 85%.[11] Ten to 15% of patients with favorable histology and 50% of patients with anaplastic tumors experience tumor progression or relapse.[11] Similar to newly diagnosed Wilms tumor, relapsed Wilms tumor is a heterogeneous disease, and current treatment strategies stratify intensity and scheduling of the treatment modalities based on prognostic features. For newly diagnosed disease, the most important prognostic features are stage and histology. Similar risk-adapted strategies are being attempted for the 15% of patients who experience relapse. Success rates after relapse range from 25%–45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse less than 6–12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases) event-free survival is less than 15%.[12] However, recent trials with HDC and autologous HCT have reported three- or four-year OS rates from 60%–73%.[13]

OSTEOSARCOMA

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Osteosarcoma is a primary malignant bone tumor that is characterized by formation of bone or osteoid by the tumor cells. Osteosarcoma occurs predominantly in the appendicular skeleton of adolescents. In children and adolescents, more than 50% of these tumors arise from bones around the knee. The prognosis of localized osteosarcoma has greatly improved over the last 30 years with OS rates increasing from 10% with surgery alone (usually amputation) to 70% with the introduction of neoadjuvant chemotherapy and limb-sparing surgery.[14] However, 30%–40% of patients with non-metastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs.[14] Mean 5-year post-relapse survival rate is approximately 28%, with some groups having a 0% OS rate. Prognostic factors for recurrence include site and size of the primary tumor, presence of metastases at the time of diagnosis, resection adequacy, and tumor response to preoperative chemotherapy (measured as percent of tumor necrosis in the resection specimen). Overall EFS for patients with metastatic disease at diagnosis is about 20%–30%.[15]

RETINOBLASTOMA

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (25% to 30%) or nonheritable (70% to 75%) tumor.[16] Cases may be unilateral or bilateral, with bilateral tumors almost always occurring in the heritable type. The type of treatment depends on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy, has a high cure rate. However, once disease has spread beyond the eye, survival rates drop significantly; five-year disease-free survival is reported to be less than 10% in those with extraocular disease, and stage 4B disease (i.e., disease metastatic to the CNS) has been lethal in virtually all cases reported.[17]

The strategy for nonmetastatic disease depends on the disease extent, but may include focal therapies (e.g., laser photocoagulation, cryotherapy, plaque radiotherapy), intravitreal chemotherapy, intra-arterial chemotherapy, systemic chemotherapy, enucleation, or a combination.[18] For metastatic disease, intensive multimodal therapy with high-dose chemotherapy, with or without radiotherapy, is standard care.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of pediatric solid tumors are typically measured in units of survival past treatment: event-free survival (EFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of peripheral neuroblastoma, Ewing's sarcoma, or any other solid childhood malignancy, clinical trials that compare this therapy with standard medical treatment (chemotherapy, and/or surgical resection with or without radiation), are needed. Further, for treatment of malignant solid tumors, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

PERIPHERAL NEUROBLASTOMA

Single Autologous Hematopoietic Cell Transplantation (HCT)

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Systematic Review

In 2013, Yalcin published a Cochrane meta-analysis on the three well-designed, randomized controlled trials (RCTs)[19-22] using autologous hematopoietic cell transplantation (HCT) in the treatment of 739 children with high-risk neuroblastoma.[23] The primary objective was to compare the efficacy of myeloablative therapy with conventional therapy. The included studies all used an age of one year as the cut-off point for pretreatment risk stratification. There was a statistically significant difference in EFS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (three studies, 739 patients; hazard ratio [HR]=0.78, 95% CI, 0.67 to 0.90). There was a statistically significant difference in OS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (two studies, 360 patients; HR=0.74, 95% CI, 0.57 to 0.98). However, when additional follow-up data were included in the analyses, the difference in EFS remained statistically significant (three studies, 739 patients; HR=0.79, 95% CI, 0.70 to 0.90), but the difference in OS was no longer statistically significant (two studies, 360 patients; HR=0.86, 95% CI, 0.73 to 1.01). The meta-analysis of secondary malignant disease and treatment-related death did not show any statistically significant differences between the treatment groups. Data from one study (379 patients) showed a significantly higher incidence of renal effects, interstitial pneumonitis, and veno-occlusive disease in the myeloablative group compared with conventional chemotherapy, whereas for serious infections and sepsis, no significant difference between the treatment groups was identified. No information on quality of life was reported.

Available evidence on the use of autologous HCT in high-risk neuroblastoma is sufficient to suggest treatment benefit with transplant.

Tandem Hematopoietic Cell Transplantation (HCT)

Systematic Review

A comparative effectiveness review was conducted on the use of hematopoietic cell transplantation in the pediatric population by the Blue Cross and Blue Shield Association Technology Evaluation Center for the Agency for Healthcare Research and Quality (AHRQ).[24] The review concluded that the body of evidence on overall survival with tandem HCT compared to single HCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.

Randomized Controlled Trials

Park (2019) reported results of an RCT that compared tandem autologous transplant to single transplant in high risk neuroblastoma patients.[25] Patients were enrolled from 2007 to 2012 at 142 Children's Oncology Group centers. Of the 652 patients enrolled, 270 were excluded due to patient choice or ineligibility and 355 were randomized 1:1 to receive tandem transplant (n = 176) or single transplant (n = 179). The primary outcome was EFS, reported as time from randomization to the occurrence of the first event (relapse, progression, secondary malignancy, or death from any cause). The median follow-up for patients without an event was 5.6 (0.6-8.9) years. Of the randomized patients, 83.7% completed the study and 5.9% were lost to follow-up after receiving therapy. The three-year EFS was 61.6% (95% confidence interval (CI), 54.3%-68.9%) in the tandem transplant group and 48.4% (95% CI, 41.0%-55.7%) in the single transplant group (1-sided log-rank p=0.006). A post-hoc analysis found no difference in three-year OS between the groups. During consolidation therapy, the two most commonly reported grade 3 or higher toxicities were mucosal (12.9%) and infections (17.4%)

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toxicities. There were 17 deaths due to toxicity during the induction and consolidation therapies combined. One limitation of this study is the large proportion of non-randomized patients, due in large part to parent or physician preference, which may lead to selection bias.

Nonrandomized Studies

Sung (2010) retrospectively analyzed the efficacy of single versus tandem autologous HCT in patients older than one year of age newly diagnosed with stage 4 neuroblastoma from 2000 to 2005 who were enrolled in the Korean Society of Pediatric Hematology-Oncology registry.[26] Patients were assigned to receive a single (n=70) or tandem (n=71) autologous HCT at diagnosis; 57 and 59 patients underwent single and tandem transplantation as scheduled, respectively. Patient characteristics between the two groups were similar with the exception of a higher proportion of patients in the tandem group having bone metastases. Median follow-up was 56 months (range 24-88 months) from diagnosis. Transplant-related mortality occurred in nine patients in the single transplant group and in eight in the tandem group (two after the first transplant and six after the second). The intent-to treat survival rate was five-year EFS for single versus tandem 31.3% +/- 11.5% and 51.2% +/- 12.4%, respectively; p=0.03. When the survival analysis was confined to the patients who proceeded to transplant, the probability of relapse-free survival (RFS) after the first transplant was higher in the tandem group than the single group with borderline significance (59.1% +/- 13.5% vs. 41.6% +/- 14.5%; p=0.099). The difference became significant when the analysis was confined to patients who did not achieve a CR prior to the first transplant (55.7% +/-17.0% vs. 0%; p=0.012). The authors concluded that tandem HCT for high-risk neuroblastoma is superior to single HCT in terms of survival, particularly in patients not in CR prior to the HCT.

Ladenstein (2008) reported on 28 years of experience for more than 4,000 transplants for primary (89%) and relapsed (11%) neuroblastoma in the European Group for Blood and Marrow Transplantation registry.[27] Procedures included single autologous (n=2,895), tandem autologous (n=455) and allogeneic HCT (n=71). The median age at the time of transplantation was 3.9 years (range 0.3-62 years), with 77 patients older than 18 years. The median follow-up time from HCT was 9 years. Transplant-related mortality (TRM) decreased over time in the registry for the patients who received autologous transplants only. The cumulative incidence of TRM was 4%, 6%, and 8%, respectively, at day 100, one year, and five years for the autologous group, and 13%, 16%, and 18%, respectively for the allogeneic group. Five-year OS for the autologous group (single and tandem) was 37% versus 25% in the allogeneic setting. Five-year OS for single versus tandem autologous HCT was 38% versus 33%, respectively (p=0.105).

Kim (2007) reported a retrospective analysis of 36 patients with high-risk (stage 3 or 4) neuroblastoma who underwent either a single autologous HCT (n=27) or a tandem autologous HCT (n=9) at Seoul National University Children's Hospital between 1996 and 2004.[28] EFS of patients who underwent double HCT was similar to that of patients who underwent a single autologous HCT (p=0.5).

George (2006) reported long-term survival data of high-risk neuroblastoma patients (n=82) treated with tandem autologous HCT between 1994 and 2002.[29] Median age at diagnosis was 35 months (range 6 months to 18 years). Three- and five-year OS were 74% (95% CI 62-82%) and 64 % (95% CI 52-74%) respectively.

von Allmen (2005) reported outcomes on 76 patients with previously untreated high-risk stage III/IV neuroblastoma treated with aggressive surgical resection with or without local radiation

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therapy followed by tandem autologous high-dose chemotherapy and stem-cell rescue.[30] Overall EFS for the series at three years was 56%.

Marcus (2003) reported outcomes in 52 children with stage 4 or high-risk stage 3 neuroblastoma treated with induction chemotherapy, surgical resection of the tumor when feasible, local radiotherapy and consolidation with tandem autologous HCT.[31] Radiotherapy was given if gross or microscopic residual disease was present prior to the myeloablative cycles (n=37). Of the 52 consecutively treated patients analyzed, 44 underwent both transplants, 6 underwent a single transplant, and 2 progressed during induction. The three-year EFS was 63%, with a median follow-up of 29.5 months.

Kletzel (2002) reported on the outcomes of 25 consecutive newly diagnosed high-risk neuroblastoma patients and one with recurrent disease, diagnosed between 1995 and 2000, and treated with triple-tandem autologous HCT.[32] After stem-cell rescue, patients were treated with radiation to the primary site. Twenty-two of the 26 patients successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Seventeen patients completed all three cycles of high-dose therapy and stem-cell rescue, two patients completed two cycles and three patients completed one cycle. There was one toxic death, and one patient died from complications of treatment for graft failure. Median follow-up was 38 months, and the three-year EFS and survival rates were 57% +/- 11% and 79% +/- 10%, respectively.

Grupp (2000) reported the outcomes of a Phase II trial that involved 55 children with high-risk neuroblastoma who underwent tandem autologous HCT.[33] Five patients completed the first HCT course but did not complete the second. There were four toxic deaths. With a median follow-up of 24 months from diagnosis, three-year EFS was 59%.

Despite the low-quality of existing evidence on the use of tandem autologous HCT for treatment of high-risk neuroblastoma, there is a suggestion of potentially increased survival with tandem transplant compared with single transplant.

Reduced Intensity Conditioning

Sung evaluated feasibility and efficacy of reduced-intensity allogeneic cell transplantation (RI alloSCT) in six children with neuroblastoma who failed tandem HDCT/autoSCT.[34] Although the regimen-related short-term toxicity was manageable in intensively pretreated patients, graft-versus-tumor effect was not sufficiently strong to control tumor progression in patients who had a significant tumor burden at transplant.

EWING’S SARCOMA AND THE EWING FAMILY OF TUMORS

During the 1980’s and 90’s, several small series, case reports, and a report from the European Bone Marrow Transplant Registry suggested that autologous HCT could improve the outcome for patients with high-risk ESFT.[35] The original policy position on Ewing’s was based on these studies and reports. Subsequent to the publication of these reports, additional evidence has been reported on the use of autologous HCT in ESFT, including a systematic review and several non-randomized studies.

Systematic Review

The AHRQ comparative effectiveness review of HCT in the pediatric population also addressed ESFT, concluding that low-strength evidence on overall survival suggests no

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benefit with single autologous HCT compared with conventional therapy for the treatment of high-risk ESFT.[24] The body of evidence on overall survival with tandem autologous HCT compared with single autologous HCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.

Nonrandomized Studies

In 2015, Jahnukainen reported their single-institution experience with high-dose thiotepa as consolidation therapy with autologous HCT for high-risk Ewing family tumors. Data from 24 patients who were treated between 1986 and 2012 were retrospectively analyzed. Ewing family tumor patients received single and tandem high-dose therapy with special emphasis on HD-thiotepa as the emphasis of the regimen. The 10-year overall survival for the entire cohort was 0.73±0.01. Thirteen out of the 24 underwent high-dose therapy (10 single, 3 tandem). There was no toxic mortality.

Early case series were characterized by small numbers of patients, and comparison of the studies was difficult for several reasons. Within each report, patients often received a variety of chemotherapeutic regimens and many of the studies did not share the same patient eligibility criteria (and in some, the definition of high risk included patients with criteria that did not result in inferior prognosis). In addition, some studies used autologous, and others allogeneic HCT.

Subsequent to the early wave of publications, in 2001, Meyers reported on a prospective study with autologous HCT in 32 patients with newly diagnosed Ewing's sarcoma metastatic to bone and/or bone marrow.[36] Induction therapy consisted of five cycles of cyclophosphamide-doxorubicin-vincristine, alternating with ifosfamide-etoposide. Twenty-three patients proceeded to the consolidation phase with melphalan, etoposide, total body irradiation, and autologous HCT (of the nineatients who did not proceed, two were secondary to toxicity and four to progressive disease). Three patients died during the high-dose phase. Two-year EFS for all eligible patients was 20% and 24% for the 29 patients who received the high-dose consolidation therapy. The study concluded that consolidation with high-dose chemotherapy (HDC), TBI, and autologous stem-cell support failed to improve the probability of EFS for this cohort of patients when compared with a similar group of patients treated with conventional therapy. The authors noted that their findings differed from some previous studies and noted that the previous studies suffered from heterogeneous patient populations. The authors concluded that future trials of autologous HCT must be conducted prospectively, with identification of a group at high risk for failure, and all patients entering the study at the same point in therapy.

Gardner reported the results of 116 patients with Ewing's sarcoma who underwent autologous HCT (80 as first-line therapy and 36 for recurrent disease) between 1989 and 2000.[37] Five-year probabilities of PFS in patients who received HCT as first-line therapy were 49% (95% CI: 30–69%) for those with localized disease at diagnosis and 34% (95% CI: 22–47%) for those with metastatic disease at diagnosis. For the population with localized disease at diagnosis and recurrent disease, five-year probability of PFS was 14% (95% CI: 3–30%). The authors concluded that PFS rates after autologous HCT were comparable to rates seen in patients with similar disease characteristics treated with conventional therapy.

Results from one group of patients in the Euro-EWING 99 trial were reported by Ladenstein for patients with primary disseminated multifocal Ewing sarcoma (PDMES).[38] From 1999 to 2005, 281 patients with PDMES were enrolled in the Euro-EWING 99 R3 study; the Euro-EWING99 Committee agreed to stop enrollment to this group and release the data. Median age was 16.2

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years (range: 0.4-49 years). Patients with isolated lung metastases were not part of the analysis. The recommended treatment consisted of induction chemotherapy, HDC and autologous HCT and local treatment to the primary tumor (surgery and/or radiation or neither). Induction therapy was completed by 250 (89%) of patients. One-hundred sixty-nine (60%) of the patients proceeded to HCT; reasons for not proceeding to HCT included disease progression or other or unknown reasons. One patient died during induction therapy from sepsis. High-dose chemotherapy TRM consisted of three patients dying within the first 100 days after high-dose therapy- one from acute respiratory distress syndrome and two from severe veno-occlusive disease and septicemia; late deaths included three patients who died 1-1.5 years after high-dose therapy. After a median follow-up of 3.8 years, score allowed allocation of patients with PDMES at diagnosis to three risk groups with the following outcomes: group 1 (score ≤3; n=82) EFS of 50%, group 2 (score >3 but <5; n=102) EFS of 25%, and group 3 (score ≥5; n=70) EFS of 10% (p<0.0001). The authors concluded that this scoring system may facilitate risk-adapted treatment strategies. The estimated three-year EFS and OS for all 281 patients were 27% +/- 3% and 34% +/- 4%, respectively. Individual risk factors were brought into a scoring model to predict outcome at diagnosis. The values of the score points were based on log-hazard ratios, and the factor with the smallest hazard ratio was assigned one point. One score point was attributed to the following risk factors: age older than 14 years, bone marrow metastases, one bone lesion and additional presence of lung metastases; 1.5 points were attributed to the risk factors of primary tumor volume ≥200 mL and more than one bone lesion.

RHABDOMYOSARCOMA

Available evidence on the use of HCT in rhabdomyosarcoma (RMS) consists of several systematic reviews summarizing a body of non-randomized trials.

Systematic Reviews

A 2010 Cochrane review of non-randomized studies, the effectiveness of HDC with stem cell rescue (SRC) versus standard-dose chemotherapy in improving event-free survival (EFS) and overall survival (OS) of children and young adults with metastatic rhabdomyosarcoma was assessed.[39] The review concluded that use of HDC with SCR as a standard therapy for children with metastatic rhabdomyosarcoma is not justified at this time. Overall, the quality and quantity of evidence is limited as no RCTs could be identified, and available non-randomized studies have significant methodological limitations, especially selection bias. The review stated that only large, prospective RCTs could answer whether HDC with SCR improves survival in rhabdomyosarcoma.

The AHRQ comparative effectiveness review noted previously also considered the use of HCT in RMS.[24] The following conclusions were offered:

- Moderate-strength evidence on overall survival suggests no benefit with single HCT compared to conventional therapy for the treatment of high-risk metastatic rhabdomyosarcoma.
- The body of evidence on overall survival with single HCT compared to conventional therapy for the treatment of high-risk rhabdomyosarcoma of mixed tumor type is insufficient to draw conclusions.
- The body of evidence on overall survival with single HCT compared to conventional therapy for the treatment of congenital alveolar rhabdomyosarcoma, cranial

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parameningeal rhabdomyosarcoma with metastasis, or the use of allogeneic transplantation for metastatic rhabdomyosarcoma was insufficient to draw conclusions.

Weigel published a systematic review on 2001 on the role of autologous HCT in the treatment of metastatic or recurrent rhabdomyosarcoma, which involved a total of 389 patients from 22 studies.[40] Based on all of the data analyzing EFS and OS, they concluded that there was no significant advantage to undergoing this type of treatment.

Nonrandomized Studies

Autologous HCT has been evaluated in a limited number of patients with “high-risk” RMS (stage 4 or relapsed) in whom complete remission (CR) is achieved after standard induction therapy. Data are relatively scarce, due in part to the rarity of the condition.

Carli conducted a prospective non-randomized study of 52 patients with metastatic RMS, who were in complete remission after induction therapy and subsequently received HDC (“megatherapy”) and autologous HCT and compared them to 44 patients who were in remission after induction therapy who subsequently received conventional chemotherapy.[41] No significant differences existed between the two study groups (i.e., no differences in clinical characteristics, induction chemotherapy received, sites of primary tumor, histologic subtype, age, or presence/extent of metastases). Three-year EFS and OS were 29.7% and 40%, respectively, for the autologous HCT group and 19.2% and 27.7%, respectively, for the group that received standard consolidation chemotherapy. The difference was not statistically significant (p=0.3 and 0.2 for EFS and OS, respectively). The median time after chemotherapy to relapse was 168 days for the autologous HCT group, and 104 days for the standard chemotherapy group (p=0.05). Therefore, although there was some delay to relapse, there was no clear survival benefit from using autologous HCT compared to conventional chemotherapy.

Klingebiel prospectively compared the efficacy of two HDC treatments followed by autologous stem-cell rescue versus an oral maintenance treatment (OMT) in 96 children with stage IV soft tissue sarcoma (88 of whom had rhabdomyosarcoma).[42] Five-year OS probability for the whole group was 0.52 + 0.14 for the patients who received OMT (n=51) and 0.27 + 0.13 for the transplant group (n=45; p=0.03). For the patients with rhabdomyosarcoma, five-year OS probability was 0.52 + 0.16 with OMT versus 0.15 + 0.12 with transplant (p=0.001). The authors concluded that transplant has failed to improve prognosis in metastatic soft tissue sarcoma, but that OMT could be a promising alternative.

McDowell reported the results of the International Society of Paediatric Oncology (SIOP) study MMT-98, for pediatric patients from 48 centers with metastatic rhabdomyosarcoma, entered into the study from 1998 to 2005.[43] There were a total of 146 patients entered, aged six months to 18 years. The patients were risk-stratified and treated accordingly. One hundred and one patients were considered poor risk patients (PRG) if they were older than 10 years of age, or had bone marrow or bone metastases. Planned therapy for the PRG was induction therapy, sequential high-dose chemotherapy and peripheral blood autologous HCT and finally, maintenance therapy. Seventy-nine of the 101 PRG patients (78.2%) underwent the high-dose therapy, after which 67.1% achieved a partial or complete response. Sixty-seven of the 101 PRG patients received local treatment: 37 radiation alone, 10 surgery alone and 20 both modalities. No treatment-related deaths were reported in the PRG. Three- and five-year EFS for the PRG group was 16.5% and 14.9%, respectively and three- and five-year OS were 23.7% and 17.9%, respectively [HR=2.46; CI: 1.51-4.03; p<0.001).

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WILMS TUMOR

Most studies of autologous HCT for high-risk Wilms tumor have been very small series or case reports.[11,13,44] A systematic review and meta-analysis have also been published and comprise the focus of this review.

Systematic Reviews

The AHRQ review discussed above also addressed HCT in pediatric patients with Wilms tumor, concluding: Low-strength evidence on overall survival suggests no benefit with single HCT compared to conventional therapy for the treatment of high-risk relapsed Wilms tumor.[24]

A meta-analysis reported on the efficacy of autologous HCT in recurrent Wilms' tumor for articles published between 1984 and 2008 that reported survival data.[45] Six studies were included for a total of 100 patients, and patient characteristics and treatment methods were similar across studies, although there was variation in the preparative regimens used.[11,13,44,46-48] Patients were between the ages of 11 months and 16 years, and had similar primary tumor stage, relapse location and time to relapse across studies. The four-year OS among the 100 patients was 54.1% (42.8-64.1%) and four-year EFS based on 79 patients was 50.0% (37.9-60.9%). A multivariate analysis found that site of relapse and histology were important predictors for survival, in that patients who did not have a lung-only relapse had more than three times the risk of death or recurrence than patients who relapsed in the lungs only, and the patients with unfavorable histology had more than twice the risk of death compared to those with favorable histology (hazard ratios 3.5 and 2.4, respectively). The authors compared the survival rates from these six studies in which the patients were treated with autologous HCT to patients treated with conventional chemotherapy between 1995 and 2002. The authors found that, in general, the chemotherapy treated patients had comparable or improved four-year survival compared to the HCT group, however, there was a suggestion that patients with lung-only stage 3 and 4 relapse may benefit from autologous HCT with a 21.7% survival advantage over the chemotherapy patients (however the ranges were very wide): four-year OS for the stage 3 and 4 patients with lung only relapse treated with HCT versus chemotherapy was 74.5% (51.7-87.7%) and 52.8% (29.7-71.5%), respectively.

Nonrandomized Studies

Malogolowkin (2017) published a retrospective analysis describing the outcomes of 253 patients with relapsed Wilms tumor (WT) who received high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplant (HCT) between 1990 and 2013 that were reported to Center for International Blood and Marrow Transplant Research.[49] The five-year estimates for event-free survival (EFS) and overall survival (OS) were 36% (95% CI; 29–43%) and 45% (95 CI; 38–51%), respectively. Relapse of primary disease was the cause of death in 81% of the population. EFS, OS, relapse, and transplant-related mortality showed no significant differences when broken down by disease status at transplant, time from diagnosis to transplant, year of transplant, or conditioning regimen. The data suggest that high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplant (HCT) for relapsed WT is well tolerated and outcomes are similar to those reported in the literature. The greatest limitation of the study is its retrospective, registry-based analyses and that the data originate from basic forms, and thus, did not include histology, site of metastases, stage of disease, genetic syndrome, tumor spillage, and radiation.

OSTEOSARCOMA

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Rare small series and case reports are available examining the use of autologous HCT in osteosarcoma.[50] Autologous HCT has been successful in inducing short-lasting remissions but has not shown an increase in survival.[14]

RETINOBLASTOMA

Localized Retinoblastoma

No studies focusing on autologous HCT for patients with localized retinoblastoma were identified.

Metastatic Retinoblastoma

Most studies of autologous HCT for metastatic retinoblastoma have been very small series or case reports.[51-56] In addition, one systematic review also addresses the use of autologous HCT in retinoblastoma.

Systematic Review

The AHRQ review considered above addressed the use of HCT in pediatric patients with retinoblastoma, concluding that available evidence on overall survival suggests no benefit with single HCT compared to conventional therapy for the treatment of extraocular retinoblastoma with central nervous system involvement.[24] The body of evidence on overall survival with single HCT compared with conventional therapy for the treatment of extraocular retinoblastoma without central nervous system (CNS) involvement was insufficient to draw conclusions. Likewise, the body of evidence on overall survival with single HCT compared with conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was also insufficient to draw conclusions.

Nonrandomized Studies

Dunkel reported the outcomes of 15 consecutive patients with stage 4a metastatic retinoblastoma who presented between 1993 and 2006 and were treated with HDC and autologous HCT.[57] Twelve patients had unilateral retinoblastoma and three had bilateral disease. Metastatic disease was not detected at the time of diagnosis, but became clinically evident at a median of six months (range: 1-82 months) post-enucleation. The patients had metastatic disease to bone marrow (n=14), bone (n=10), the orbit (n=9) and/or the liver (n=4). Two patients progressed prior to HCT and died. Thirteen patients underwent HCT, and 10 are retinoblastoma-free in first remission at a median follow-up of 103 months (range: 34-202 months). Three patients recurred 14-20 months post-diagnosis of metastatic disease, (two in the CNS and one in the mandible), and all died of their disease. Five-year retinoblastoma-free and event-free survival were 67% (95% CI 38-85%) and 59% (31-79%), respectively. Six of the 10 patients who survived received radiation therapy. Three patients developed secondary osteosarcoma at 4, 9 and 14 years after diagnosis of metastatic disease, two in previously irradiated fields and one in a non-irradiated field. The authors concluded that HCT was curative for the majority of patients treated in their study with stage 4a retinoblastoma.

Dunkel reported the outcomes of eight patients diagnosed with stage 4b retinoblastoma between 2000 and 2006 treated with autologous HCT.[17] Seven of the patients had leptomeningeal disease and one had only direct extension to the CNS via the optic nerve. At the time of diagnosis of intra-ocular retinoblastoma, three patients already had stage 4b disease; the other five patients developed metastatic disease at a median of 12 months (range

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3-69 months). Two patients progressed prior to HCT and one patient died of toxicity during induction chemotherapy. Of the five patients that underwent HCT, two were event-free at 40 and 101 months. One of the event-free survivors received radiation therapy (external beam plus intrathecal radioimmunotherapy) and the other did not receive any form of radiation. Three patients had tumor recurrence at 3, 7, and 10 months post-HCT. The authors concluded that HCT may be beneficial for some patients with stage 4b retinoblastoma, but that longer follow-up is necessary to determine whether it is curative in this population.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published consensus guidelines for clinically appropriate indications for hematopoietic cell transplantation (HCT) based on best prevailing evidence. The following was excerpted from original publication.[58] Indications for HCT in pediatric patients with the solid tumors types addressed in this review are outlined in Table 1.

Table 1. ASBMT Indications for HCT in Pediatric Patients with Solid Tumors[58]

Indication and Disease Status	Allogeneic HCT[a]	Autologous HCT[a]
Ewing sarcoma, high risk or relapse	D	S
Soft tissue sarcoma, high risk or relapse	D	D
Neuroblastoma, high risk or relapse	D	S
Wilms tumor, relapse	N	C
Osteosarcoma, high risk	N	C

ASBMT: American Society for Blood and Marrow Transplantation; HCT: hematopoietic cell transplantation.
[a] "Standard of care (S): This category includes indications that are well defined and are generally supported by evidence in the form of high quality clinical trials and/or observational studies (eg, through CIBMTR or EBMT)." "Standard of care, clinical evidence available (C): This category includes indications for which large clinical trials and observational studies are not available. However, HCT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. HCT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as 'Standard of Care'." "Developmental (D): Developmental indications include diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option. HCT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as 'Standard of Care, Clinical Evidence Available' or 'Standard of Care'." "Not generally recommended (N): Transplantation is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT. The effectiveness of non-transplant therapies for an earlier phase of a disease does not justify the risks of HCT. Alternatively, a meaningful benefit is not expected from the procedure in patients with an advanced phase of a disease. However, this recommendation does not preclude investigation of HCT as a potential treatment and transplantation may be pursued for these indications within the context of a clinical trial."

NATIONAL COMPREHENSIVE CANCER NETWORK

For Ewing sarcoma, the National Comprehensive Cancer Network (NCCN) guidelines for bone cancer (v.1.2020) state the following:[59]

"High-dose chemotherapy followed by stem cell transplant (HDT/SCT) has been evaluated in patients with localized as well as metastatic disease. HDT/SCT has been associated with potential survival benefit in patients with non-metastatic disease. However, studies that have

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evaluated HDT/SCT in patients with primary metastatic disease have shown conflicting results…. HDT/SCT has been associated with improved long-term survival in patients with relapsed or progressive Ewing sarcoma in small, single-institution studies. The role of this approach is yet to be determined in prospective randomized studies."

SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Single Autologous Hematopoietic Cell Transplantation

It appears that the use of autologous hematopoietic cell transplantation may improve overall health outcomes when used to for initial treatment of high-risk Ewing's sarcoma, to consolidate remissions or treat residual, recurrent or refractory Ewing's sarcoma. Therefore, allogeneic HCT may be considered medically necessary in this population.

There is enough research to show improved event-free survival (EFS) and overall survival (OS) with use of single autologous hematopoietic cell transplantation (HCT) for treatment of children with neuroblastoma as first-line treatment, or as treatment of recurrent or refractory neuroblastoma. Therefore, use of single autologous HCT may be considered medically necessary in this population.

There is enough research to show that there is a potential benefit of hematopoietic cell transplantation (HCT) in some high-risk, relapsed Wilms tumor patients; therefore use of autologous HCT in this population may be considered medically necessary.

It appears that autologous hematopoietic cell transplantation (HCT) may improve overall health outcomes for some people with metastatic retinoblastoma. Therefore use of autologous HCT in this population may be considered medically necessary.

There is not enough research to show that autologous hematopoietic cell transplantation (HCT) is beneficial in the initial treatment of low- or intermediate risk Ewing's sarcoma family of tumors (ESFT), initial treatment of low- or intermediate-risk neuroblastoma, or other solid tumors of childhood, including but not limited to osteosarcoma, retinoblastoma without metastasis, rhabdomyosarcoma, and Wilms tumor, other than recurrent, high-risk. Therefore, use of autologous HCT in this population is considered investigational.

Tandem Autologous Hematopoietic Cell Transplantation

Few studies directly comparing single autologous to tandem autologous hematopoietic cell transplantation (HCT) for high-risk neuroblastoma have been published; however, the evidence suggests that the use of tandem autologous for high-risk neuroblastoma may result in event-free survival (EFS) rates superior to those reported with the use of single autologous HCT. Therefore, for pediatric patients with high-risk neuroblastoma who meet the criteria, treatment with tandem HCT may be considered medically necessary.

There is not enough research to show that tandem autologous hematopoietic cell transplantation (HCT) is beneficial in the treatment of pediatric solid tumors other than high-risk neuroblastoma. Therefore, with the exception of high-risk neuroblastoma, use of tandem autologous HCT is considered investigational for the treatment of pediatric solid tumors.

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ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

There is not enough research to show that allogeneic hematopoietic cell transplantation (HCT) is beneficial in the treatment of pediatric solid tumors, including tumors that relapse after autologous transplant or fail to respond. Therefore, use of allogeneic HCT in the treatment of pediatric solid tumors is considered investigational.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose

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	chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Medical Policy Manual Transplant, Policy No. 45.38

Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Effective: November 1, 2019

Next Review: August 2020
Last Review: September 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Single autologous hematopoietic cell transplantation may be considered **medically necessary** in the treatment of germ-cell tumors for either of the following (A. or B.):

   A. For patients with *favorable prognostic factors* that have failed a previous course of conventional-dose salvage chemotherapy. Patients with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response to initial chemotherapy, low levels of serum markers, and low volume disease.

   B. For patients with *unfavorable prognostic factors* as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease. Patients with unfavorable prognostic factors are those with an incomplete response to initial therapy or relapsing mediastinal nonseminomatous germ-cell tumors.

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II. Tandem autologous hemopoietic cell transplantation or transplant with sequential high-dose chemotherapy may be considered **medically necessary** in the treatment of testicular tumors, either as salvage therapy or for those with platinum-refractory disease.

III. Hematopoietic cell transplantation is considered **investigational** in the treatment of germ-cell tumors for any of the following:

   A. Autologous hemopoietic cell transplantation as a component of first-line treatment for germ-cell tumors.

   B. Tandem autologous hemopoietic cell transplantation or transplant with sequential high-dose chemotherapy for all other germ-cell tumors of any stage not addressed in Criterion II.

   C. Allogenic hemopoietic cell transplantation for any germ-cell tumors, including, but not limited to its use as therapy after failed autologous hematopoietic cell transplantation.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer, Transplant, Policy No. 45.26
4. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27

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5. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body radiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are

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susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but usually not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

GERM-CELL TUMORS

Germ-cell tumors are composed primarily of testicular neoplasms (seminomas or nonseminomatous tumors) but also include ovarian and extragonadal germ-cell tumors (e.g., retroperitoneal or mediastinal tumors). Germ-cell tumors are classified according to their histology, stage, prognosis, and response to chemotherapy.

Histologies include seminoma, embryonal carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed germ-cell tumors. Seminomas are the most common; all other types are collectively referred to as nonseminomatous germ-cell tumors.

Stage is dependent on location and extent of the tumor, using the American Joint Committee on Cancer’s TNM system. TNM stages, modified by serum concentrations of markers for tumor burden (S0-3) when available, are grouped by similar prognoses. Markers used for germ-cell tumors include human beta-chorionic gonadotropin (B-hCG), lactate dehydrogenase (LDH), and alpha fetoprotein (AFP). However, most patients with pure seminoma have normal AFP concentrations. For testicular tumors, Stages IA-B have tumors limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); Stages IIA-C have increasing size and number of tumor-involved lymph nodes, and at least one marker moderately elevated above the normal range (S1); and Stages IIIA-C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

Germ-cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, and extent of primary tumor, and on serum marker levels. Good-risk pure seminomas can be at any primary site, but are without nonpulmonary visceral metastases or marker elevations. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated hCG and/or LDH. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated AFP (due to mixture with nonseminomatous

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components) are managed as nonseminomatous germ-cell tumors. Good- and intermediate-risk nonseminomatous germ-cell tumors have testicular or retroperitoneal tumors without nonpulmonary visceral metastases, and either S1 (good risk) or S2 (intermediate) levels of marker elevations. Poor-risk tumors have mediastinal primary tumors, or nonpulmonary visceral metastases, or the highest level (S3) of marker elevations.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of germ-cell tumors are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of testicular cancer or any other germ-cell tumor, comparative clinical trials that compare this therapy with standard medical treatment, such as standard chemotherapy regimens, are needed. Further, for treatment of germ-cell tumors, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION AS FIRST-LINE THERAPY

Randomized Controlled Trials

Daugaard (2011) reported the outcomes of a randomized Phase III study comparing standard-dose BEP (cisplatin, etoposide, and bleomycin) to sequential high-dose VIP (cisplatin, etoposide, and ifosfamide) plus stem-cell support in previously untreated males with poor-prognosis germ-cell cancer.[1] The study aimed to recruit 222 patients but closed with 137 patients from 27 European oncology centers due to slow accrual. Patients were age 15-50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ-cell tumor of either testicular or extragonadal origin. Median follow-up was 4.4 years 66 patients in the BEP group and 65 patients in the transplant group were included in the analysis. Toxicity was more severe in the patients who received high-dose chemotherapy, and toxic death was reported in two patients who received high-dose chemotherapy and one in the BEP arm. There was no improvement in complete response rate in the high-dose chemotherapy arm versus the standard-dose arm (44.6% vs. 33.3%, respectively, p=0.18). There was no difference in failure-free survival between the two groups. At two years, failure-free survival was 44.8% (95% confidence interval [CI]: 32.5-56.4) and 58.2% (95% CI: 48.0-71.9), respectively for the standard and high-dose arms. The difference was not statistically significant (p=0.06). Overall survival did not differ between the two groups (log-rank p>0.1). The authors concluded that high-dose chemotherapy given as part of first-line therapy does not improve outcomes in patients with poor-prognosis germ-cell tumor.

Motzer (2007) reported on a Phase III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ-cell tumors.[2] The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (four cycles of standard BEP) (n=111), or two cycles of BEP followed by two cycles of high-dose chemotherapy with autologous HCT. Median follow-up was 51 months. One-year durable complete response rate was 52% after BEP and high-dose chemotherapy with HCT, and 48% after BEP alone (p=0.53). There was no survival difference at 106 months for patients treated

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with high-dose chemotherapy and HCT compared to the patients treated with conventional chemotherapy (68% and 69%, respectively).

Droz (2007) assessed the impact of high-dose chemotherapy with HCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ-cell tumors.[3] Patients were randomized to four cycles every 21 days of vinblastine, etoposide, cisplatin and bleomycin (n=57) or a slightly modified regimen followed by high-dose chemotherapy and autologous HCT (n=57). In an intention-to-treat analysis, there were 56% and 42% complete responses in the conventional and high-dose chemotherapy groups, respectively (p=0.099). Median follow-up was 9.7 years, and no significant difference between OS was observed (p=0.167).

AUTOLOGOUS HCT FOR RELAPSED OR REFRACTORY GERM-CELL TUMORS

Randomized Controlled Trial

In 2005, Pico reported on a randomized trial comparing four cycles of conventional-dose chemotherapy to three cycles of the same regimen followed by carboplatin-based high-dose chemotherapy plus autologous HCT in 280 patients who had relapsed after a complete or partial remission following first-line therapy with a cisplatin-based regimen.[4] The authors reported no significant differences between treatment arms in three-year event-free survival (EFS) and OS. However, the study began before international consensus established the current risk group definitions;[5] thus, Pico and colleagues likely included some patients now considered to have good prognosis at relapse. Furthermore, while 77% and 86% of patients in the control and experimental arms, respectively, had at least one elevated serum tumor marker, they did not report how highly elevated these were and did not compare arms with respect to the marker thresholds that presently determine risk level (S1-3). Finally, high-dose chemotherapy in the experimental arm followed three cycles of conventional-dose chemotherapy, which differs from most current practice in the U.S., where a single cycle is used prior to high-dose chemotherapy. As a consequence, 38 of 135 (28%) randomized to the high-dose chemotherapy arm did not receive high-dose chemotherapy because of progression, toxicity, or withdrawal of consent.

Nonrandomized Studies

Zschäbitz (2018) reported a retrospective analysis of the experience of two referral centers using high dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT) for relapsed or refractory germ cell tumors.[6] Forty-six patients treated with HDCT/ASCT between 2000–2016 were identified; 52% of whom were categorized as poor risk by the International Prognostic Factors Study Group (IPFSG) prognosis score. HDCT/ASCT was performed as the first salvage regimen in 67% of patients. Further consolidation therapy after HDCT/ASCT was performed with 41% of patients undergoing resection of residual tumor. In patients who were in complete remission after HDCT/ASCT and in those who received residual tumor resection or radiotherapy as consolidation median progression free survival (mPFS) was 17.7 months (range 2–185; 95% CI: n.a.) and median overall survival (mOS) had not been reached with 64% of patients being alive at a median follow up time of 41 months. Median PFS and OS in patients who did not achieve a complete response was 3.3 months (95% CI: 1 1.0–5.5) and 6.4 months (95% CI: 5.6–7.2) in those who had no further consolidation treatment.

Adra (2017) reported a retrospective analysis of a single institution experience of using high dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT) for relapsed or

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refractory germ cell tumors.[7] Between 2004 and 2014, there were 364 consecutive patients with germ cell tumors who progressed after cisplatin-based combination chemotherapy; 341 received two consecutive courses of HDCT consisting of 700 mg/m2 carboplatin and 750 mg/m2 etoposide, each for three consecutive days, and each followed by peripheral blood stem cell transplant. At a median follow-up of 3.3 years, patients with pure seminoma had the highest cure rate, with a two-year PFS of 90% (95% CI, 81% to 95%). Remissions were achieved in poor prognosis patients who received HDCT as third-line or subsequent therapy (two-year PFS, 49%) and in patients with platinum-refractory disease (two-year PFS, 33%). Adverse events were notable with nine treatment related deaths due to infectious complications, hepatic failure and secondary leukemia.

In 2015, Nieto reported on 43 male patients with poor-risk relapsed or refractory germ cell tumors with received high-dose chemotherapy (HDC) and autologous HCT.[8] Primary tumors were testicular in 32 patients, mediastinal in 7 patients, and retroperitoneal in 4 patients. Median follow-up was 46 months (range, 9-84 months). At follow-up, the relapse-free survival rate was 55.8% and the OS rate was 58.1%. Relapse-free survival rates were 66% in patients with testicular primaries, 28.5% in patients with mediastinal primaries and 25% in patients with retroperitoneal primaries.

In 2014, Berger reported on a retrospective comparison of 143 patients with relapsed or refractory germ-cell cancer undergoing first salvage treatment with conventional-dose (CD-CX, n=48) or high-dose chemotherapy with autologous cell transplantation (HD-CX, n=95).[9] The aim of the study was to evaluate prognostic risk factors according to the International Prognostic Factors Study Group (IPFSG) criteria and the efficacy of salvage treatment. The IPFSG categories (very low risk 13/143, low risk 36/143, intermediate risk 66/143, high risk 22/143, and very high risk 6/143) significantly correlated with OS (p=0.025) after initial salvage treatment. Vital carcinoma found in secondary resected lesions was more prevalent following CD-CX compared to HD-CX, 22/29 vs. 22/45, (p=0.021) respectively. In addition, second relapse rate was higher in the CD-CX group (75%) compared to the HD-CX group (44%), resulting in a shorter median PFS (8 vs.42 months); however, no difference in OS was observed between treatment groups.

Baek (2013) reported results of a small feasibility study of HDC followed by HCT for patients with relapsed or progressed CNS germ-cell tumors.[10] The authors enrolled 11 patients with nongerminomatous (i.e., nonseminomatous) germ-cell tumors and 9 patients with germinomatous stem-cell tumors, all of whom had received conventional chemotherapy with or without radiation before HCT. Sixteen patients received an initial course of HDC with carboplatin, thiopental, and etoposide followed by HCT, and nine of those received a second course of HDC with cyclophosphamide-melphalan followed by a second HCT. Twelve patients were alive at a median follow-up of 47 months (range, 22-90 months), with a probability of three-year OS of 59.1% (± 11.2%).

Seftel (2011) conducted a multicenter cohort study of consecutive patients undergoing a single autologous HCT for germ-cell tumor between January 1986 and December 2004.[11] Of 71 subjects, median follow-up was 10.1 years. The median age was 31 years (range 16–58 years). A total of 67 of the patients had nonseminomatous germ-cell tumors and 4 had seminomatous germ-cell tumors. A total of 57 patients had primary gonadal disease and 14 had primary extragonadal disease. Of the latter, 11 patients presented with primary mediastinal disease, 2 presented with primary central nervous system disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HCT for

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relapsed disease after achieving an initial complete response (CR). Of these, 24 patients underwent autologous HCT after a first relapse, whereas 4 patients underwent transplant after a second relapse. An additional 36 patients achieved only an incomplete response after initial therapy and proceeded to autologous HCT after salvage chemotherapy for active residual disease. Overall survival at five years was 44.7% (95% CI: 32.9–56.5%) and EFS 43.5% (95% CI: 31.4–55.1%). There were 7 (10%) treatment-related deaths within 100 days of transplant. Three (4.2%) patients developed secondary malignancies. Of 33 relapses, 31 occurred within two years of the transplant. Two very late relapses occurred 13 and 11 years after transplant. In a multivariate analysis, a favorable outcome was associated with International Germ Cell Consensus Classification (IGCCC) good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Agarwal (2009) reported their experience at Stanford in treating 37 consecutive patients who received high-dose chemotherapy and autologous HCT between 1995 and 2005 for relapsed germ-cell tumors.[12] The median patient age was 28 years (range: 9–59 years), with 34 males and 3 females. Primary tumor sites included 24 testes/adnexal, 10 chest/neck/retroperitoneal, and 3 central nervous system (CNS). Twenty-nine of the patients had received prior standard salvage chemotherapy. Three-year OS was 57% (95% CI: 41-71%) and three-year progression-free survival was 49% (95% CI: 33–64%).

TANDEM AUTOLOGOUS HCT AND SEQUENTIAL HDC FOR GERM CELL TUMORS

Systematic Review

A comparative effectiveness review conducted for the Agency for Healthcare Research and Quality (AHRQ) on the use of HCT in the pediatric population concluded that, for germ-cell tumors, the body of evidence on overall survival with tandem HCT compared with single HCT for the treatment of relapsed pediatric germ-cell tumors was insufficient to draw conclusions.[13]

Nonrandomized Studies

Lazarus (2007) reported the results of autologous HCT in relapsed testicular/germ-cell cancer from registry data from the Center for International Blood and Marrow Transplant Research.[14] Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in eight countries who received either a single transplant or tandem autologous HCT between 1989 and 2001. Of the 300 patients, 102 received tandem, and 198 single planned autologous HCT. PFS and OS at one, three, and five years was similar for both groups. The probability of PFS at five years for the tandem transplant group was 34% (95% CI: 25–44%) versus 38% (95% CI: 31–45%) in the single transplant group; p=0.50. The probability of five-year OS was 35% (95% CI: 25–46%) versus 42% (95% CI: 35–49%), respectively; p=0.29.

Lorch (2007) compared single versus sequential HDC with autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors.[15] Between November 1999 and November 2004, patients planned to be recruited in a prospective, randomized, multicenter trial comparing one cycle of cisplatin, etoposide and ifosfamide (VIP) plus three cycles of high-dose carboplatin and etoposide (CE; arm A) versus three cycles of VIP plus one cycle of high-dose carboplatin, etoposide and cyclophosphamide (CEC; arm B). The majority of the tumors were gonadal primaries; ten percent of patients in arm A had retroperitoneal, mediastinal or CNS primaries, and 11% of patients in arm B had retroperitoneal or mediastinal primaries. This represented the first salvage therapy received in

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86% of the patients in arm A and 85% in arm B, whereas 14% (arm A) and 15% (arm B) had received one or more previous salvage regimens prior to randomization. One-hundred-eleven (51%) of 216 patients were randomly assigned to sequential high-dose therapy, and 105 (47%) of 216 patients were randomly assigned to single high-dose therapy. The study was stopped prematurely after recruitment of 216 patients as a result of excess treatment-related mortality in arm B. There was a planned interim analysis after the inclusion of 50% of the required total number of patients. Survival analyses were performed on an intent-to-treat basis.

With a median follow-up time of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression free. At one year, event-free, progression-free, and overall survival rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B ($p > 0.05$ for all comparisons). Survival rates were not reported separately by primary site of the tumor. No difference in survival probabilities was found between the single and sequential high-dose regimens; however, sequential high-dose therapy was better tolerated and resulted in fewer treatment-related deaths. Treatment-related deaths, mainly as a result of sepsis and cardiac toxicity, were less frequent in arm A (four of 108 patients, 4%) compared with arm B (16 of 103 patients, 16%; $p < 0.01$). The authors state that the higher treatment-related deaths observed in arm B likely were due to the higher dosages per HCT cycle in the arm B regimen compared to arm A, and the toxic renal and cardiac effects of cyclophosphamide used in arm B. The authors conclude that sequential treatment at submaximal doses of carboplatin and etoposide might be less toxic and safer to deliver HCT in pretreated patients with germ cell tumors than single HCT.

Long-term results from this study reported five-year PFS as 47% (95% CI, 37%-56%) in arm A and 45% (95% CI, 35%-55%) in arm B (hazard ratio, 1.16; 95% CI, 0.79-1.70; p=.454). Five-year OS was 49% (95% CI, 40%-59%) in arm A and 39% (95% CI, 30%-49%) in arm B (hazard ratio, 1.42; 95% CI, 0.99-2.05; p=.057). The authors concluded that patients with relapsed or refractory germ-cell tumors can achieve durable long-term survival after single as well as sequential HCT and that fewer early deaths related to toxicity translated into superior long-term OS after sequential HCT.[16]

Lotz (2005) reported the results of a Phase II study on three consecutive cycles of high-dose chemotherapy regimens supported by autologous HCT in 45 poor-prognosis patients with relapsed germ-cell tumors.[17] From March 1998 to September 2001 (median follow-up, 31.8 months), 45 patients (median age, 28 years) were enrolled. Most of the patients (76%) had testicular primaries; 13% had mediastinal primaries; 11% retroperitoneal, hepatic or unknown. Of all patients, 22 received the complete course. Twenty-five patients died from progression and five from toxicity. The overall response rate was 37.7%, including an 8.9% complete response rate. The median OS was 11.8 months. The three-year survival and PFS rate was 23.5%. The authors used the “Beyer” prognostic score to predict the outcome of high-dose chemotherapy and concluded that patients with a Beyer score greater than two did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant/refractory primary mediastinal germ cell tumors do not benefit from high-dose chemotherapy. The authors also state that better selection criteria have to be fulfilled in forthcoming studies.

Einhorn (2007) reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with two consecutive cycles of high-dose chemotherapy for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy.[18] Patients with primary mediastinal nonseminomatous germ cell tumors or

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tumors with late relapse (two or more years after previous therapy) were excluded. The patient population included those with initial International Germ Cell Cancer Collaborative Group (IGCCCG) stage defined as low risk (39%), intermediate risk (21%) and high risk (41%), and both platinum-sensitive and refractory disease at the beginning of high-dose chemotherapy. Results from this experienced center showed that of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy (i.e., first salvage setting), 94 (70%) were disease-free during follow-up; 22 (45%) of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 (45%) were disease-free.

Letters to the editor regarding the Einhorn study noted the lack of a validation set for the prognostic scoring system used in the study, the unanswered question of the role of high-dose versus conventional-dose chemotherapy in the first salvage setting, and the lack of a universally accepted prognostic scoring system in this setting.[19]

In a subsequent study from the same center as the Einhorn study, Suleiman (2013) evaluated the outcomes for 12 patients, excluded from the previous study, with recurrent primary mediastinal nonseminomatous germ-cell tumors after initial treatment with cisplatin-containing combination chemotherapy, who were treated with tandem HCT.[20] Patients received two consecutive courses of HDC (carboplatin and etoposide) followed by HCT. Overall outcomes were poor, with a median survival of 11 months (range, 4-52 months), but 3 of 12 patients achieved a complete remission (CR; 10, 15, and 50 months' duration). One patient remained free of disease at 50 months of follow up, and one remained free of disease after tandem HCT and subsequent mediastinal surgery at 52 months of follow-up.

Pal (2013) reported five-year follow up results from a retrospective case series of 48 patients with relapsed germ-cell tumors who were enrolled in a study to evaluate the effectiveness of two sequential cycles of HDC (paclitaxel, etoposide, and carboplatin in the first cycle, followed by dose of high-dose paclitaxel, ifosfamide, and carboplatin) followed by HCT.[21] Forty-three patients (91.5%) had nonseminomatous histology. Most patients (n=39) had received two prior chemotherapy regimens; six patients had received three prior regimens. Thirty-four patients had intermediate risk classification by the Beyer score and the remainder had high risk classification. Of the 48 patients enrolled, 17 received only one course of HDC, 11 due to progressive disease, 5 due to toxicities, and 1 due to a severe fungal infection. A total of 17 patients of the 48 enrolled were alive and progression-free at a median of 123.2 months (range, 51.6- 170.2 months); 25 died, most (n=23) due to disease progression. Of the 23 patients who were alive after receiving per-protocol therapy, 18 were contacted for interviews at a median 115.6 months (range, 38.9- 185.9 months) post-enrollment and underwent a cancer-related quality-of-life assessment with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30). The overall average score on the questionnaire was 87.04 (standard deviation=14.64); the authors compared quality-of-life scores in this cohort to a separate cohort of 150 patients with germ-cell tumors who received chemotherapy, and reported that patients in their cohort had significantly higher global health scores (87.04 vs 75.62, p=0.02), but lower physical functioning scores (68.9 vs 92.7, p=0.0001.) The authors conclude that tandem HDC followed by HCT is a reasonable option for relapsed germ-cell tumors, with long-term survivors demonstrating a reasonable quality of life.

ALLOGENEIC HCT FOR GERM-CELL TUMORS

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No RCTs or nonrandomized comparative studies evaluating allogeneic HCT for germ cell tumors were identified. One 2007 case report described successful treatment of a refractory mediastinal gem cell tumor with allogeneic HCT.[22]

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, guidelines by the American Society for Blood and Marrow Transplantation were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on use of HCT within and outside of the clinical trial setting.[23] Recommendations on germ cell tumors are listed in Table 1.

Table 1. ASBMT Recommendations on Allogeneic and Autologous HCT

Indications	Allogeneic HCT	Autologous HCT
Pediatric		
Germ cell tumor, relapse	D	C
Germ cell tumor, refractory	D	C
Adult		
Germ cell tumor, relapse	N	C
Germ cell tumor, refractory	N	C

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available, standard of care; D: developmental (ie promising); HCT: hematopoietic cell transplantation N: not generally recommended.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

Guidelines from NCCN (1.2019) offer the following on the use of HCT in testicular cancer:[24]

> *All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.*
>
> In patients requiring second-line therapy for metastatic germ cell tumors, recommendations include administration of specific-high dose chemotherapy regimens with peripheral blood stem cell support at 14- to 21-day intervals for three cycles.

SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

It appears that autologous hematopoietic cell transplantation (HCT) may improve long-term event-free and overall survival rates help when included as a component of salvage treatment for people with germ-cell tumors. Therefore, single autologous hematopoietic cell transplantation may be considered medically necessary as salvage therapy for germ-cell tumors in patients who meet policy criteria.

There is not enough research to know if or how well autologous hematopoietic cell transplantation (HCT) works as a first line therapy to treat people with germ-cell tumors. This does not mean that it does not work, but more research is needed to know. Therefore, use of autologous HCT as first-line therapy is considered investigational.

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TANDEM AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION AND TRANSPLANT WITH SEQUENTIAL HIGH-DOSE CHEMOTHERAPY

It appears that tandem autologous hematopoietic cell transplantation (HCT) or transplant with sequential high-dose chemotherapy may improve overall health outcomes for patients with testicular tumors as a salvage therapy, or for those with platinum-refractory disease. Therefore, tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered medically necessary when policy criteria are met. Due to a lack of evidence and clinical practice guidelines, use of tandem autologous HCT or transplant with sequential high-dose chemotherapy as a treatment for other germ-cell tumors is considered investigational.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

There is not enough research to know if or how well allogeneic hematopoietic cell transplantation (HCT) works to improve overall health outcomes for people with germ-cell tumors. This does not mean that it does not work, but more research is needed to know. Therefore, use allogeneic HCT as first-line therapy for any germ-cell tumors is considered investigational.

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25. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors." Policy No. 8.01.35

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global

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	definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Transplant, Policy No. 45.40

Hematopoietic Cell Transplantation for Light-Chain (AL) Amyloidosis or Waldenström Macroglobulinemia

Effective: September 1, 2020

Next Review: April 2021
Last Review: July 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** for any of the following:
   A. Light chain (AL) amyloidosis
   B. As salvage therapy for chemosensitive Waldenström macroglobulinemia.

II. Autologous hematopoietic cell transplantation is considered **not medically necessary** as a therapy for chemoresistant Waldenström macroglobulinemia.

III. Autologous hematopoietic cell transplantation is considered **investigational** as a first-line treatment for Waldenström macroglobulinemia.

IV. Allogeneic hematopoietic cell transplantation is considered **investigational** for Light-chain (AL) amyloidosis and Waldenström macroglobulinemia.

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NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Light chain (AL) amyloidosis was previously known as primary systemic amyloidosis.

DEFINITIONS

consolidation therapy - Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.

relapse - The return of a disease or the signs and symptoms of a disease after a period of improvement.

salvage therapy - Treatment that is given after the cancer has not responded to other treatments.

tandem transplant – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23
4. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Transplant, Policy No. 45.30

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

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Although cord blood is an allogeneic source, the cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome six. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to be delivered at doses that could otherwise not be given without stem cells, which are infused to “rescue” hematopoiesis after high dose therapy. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this policy, the term reduced-intensity conditioning will

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refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

LIGHT CHAIN (AL) AMYLOIDOSIS

The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified on the basis of the type of amyloidogenic protein involved, as well as by the distribution of amyloid deposits. In systemic amyloidosis, the unnatural protein is produced at a site that is remote from the site(s) of deposition, whereas in localized disease the protein is produced at the site of deposition. AL amyloidosis, previously known as primary systemic amyloidosis, is the most common type of systemic amyloidosis. The amyloidogenic protein in AL amyloidosis is an immunoglobulin (Ig) light chain or light chain fragment that is produced by a clonal population of plasma cells in the bone marrow. Deposition of AL amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

Historically, this disease has had a poor prognosis, with a median survival from diagnosis of about 12 months, although outcomes have improved with the advent of combination chemotherapy with alkylating agents and autologous HCT. Emerging approaches include the use of immunomodulating drugs such as thalidomide or lenalidomide, and the proteasome inhibitor bortezomib. Regardless of the approach chosen, treatment of AL amyloidosis is aimed at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. The therapeutic index of any chemotherapy regimen is a key consideration in the context of underlying organ dysfunction.

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia (WM) is a rare B-cell malignancy. Median survival of WM ranges from five to ten years, with age, hemoglobin concentration, serum albumin level, and beta-2 microglobulin level as predictors of outcome. The Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification and a consensus group formed at the Second International Workshop on WM recognize WM primarily as a lymphoplasmacytic lymphoma (LPL) with an associated immunoglobulin M (IgM) monoclonal gammopathy.[1] The definition also requires the presence of a characteristic pattern of bone marrow infiltration with small lymphocytes demonstrating plasmacytic differentiation with variable cell surface antigen expression. The Second International Workshop indicated no minimum serum concentration of IgM is necessary for a diagnosis of WM.

Treatment of WM is indicated only in symptomatic patients and should not be initiated solely on the basis of serum IgM concentration.[2]

EVIDENCE SUMMARY

The principal outcomes associated with treatment of primary systemic amyloidosis or WM are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and

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overall survival (OS), the period of time the patient remains alive following treatment. Patient quality of life (QOL) may be another primary outcome, particularly among patients living with refractory disease. Ideally, the impact of hematopoietic cell transplantation on the treatment of these conditions is best understood in well-designed randomized controlled trials (RCT) that compare this therapy to standard medical treatment, such as conventional standard-dose chemotherapy. Further, for treatment of malignant cancers, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

AL AMYLOIDOSIS

Several clinical trials, including an RCT, and several non-comparative case series, and registry reports have been reported on the use of autologous hematopoietic cell transplantation (HCT) in patients with AL amyloidosis. To date, no evidence from clinical trials has been identified on the use of allogeneic HCT for treatment of AL amyloidosis.

Randomized Controlled Trials

One randomized multicenter trial involving eight centers from the Myelome Autogreffe (MAG) and Intergroupe Francophone du Myelome (IFM) Intergroup compared conventional chemotherapy with melphalan plus dexamethasone with myeloablative melphalan followed by autologous HCT in patients with AL amyloidosis.[3] Patients between 18 and 70 years of age with a histological diagnosis of AL amyloidosis and either a complete hematologic response characterization of amyloid deposits or evidence of a monoclonal Ig protein in the serum or urine or a monoclonal staining pattern of bone marrow plasma cells, and history of no more than two courses of any chemotherapy regimen. They were stratified according to age (younger than 65 years or 65 years or older) and according to the affected organ system (cardiac, renal, neurological, or other) and randomly allocated. Patients in the melphalan plus dexamethasone group (n=50) received monthly courses of dose-adjusted (according to cytopenic status) oral melphalan, 10 mg/m^2 of body-surface area, on days one to four plus oral dexamethasone, 40 mg/day on days one to four, for up to 18 courses if no severe adverse events occurred. In the autologous HCT patients (n=50), hematopoietic stem cells were obtained from peripheral blood with granulocyte colony-stimulating factor mobilization. Melphalan was administered intravenously on day zero, and stem cells were infused on day two, with the dose reduced from 200 mg/m^2 to 140 mg/m^2 for patients aged 65 years or older and for those with an LVEF <30%, a calculated creatinine clearance <30 mL/min, or severe liver disease. According to intention-to-treat analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 PR (28%) in the melphalan-dexamethasone recipients versus 11 CR (22%) and seven PR (14%) in the autologous HCT group (p=0.11).

At publication of the study, the median follow-up for the entire cohort was 24 months, and for survivors it was 36 months; 20 patients in the melphalan-dexamethasone group had died versus 31 in the autologous HCT group. Among 65 patients who could be evaluated, the intention-to-treat median survival for patients assigned to melphalan plus dexamethasone was 56.9 months, versus 22.2 months in the autologous HSCT group (p=0.04). Survival rates and duration were significantly better in responders (CR plus PR) compared to NR (p<0.0001). Analysis of patients who survived for at least six months and who received their assigned treatment, showed no significant difference in survival rates in patients assigned to melphalan plus dexamethasone compared to autologous HCT, with neither group reaching median survival after 80 months (p=0.38).

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This randomized trial suggests that autologous HCT may be no more efficacious than conventional chemotherapy in prolonging survival among patients with AL amyloidosis. However, the results are limited by the size of the study, a lack of assessor blinding or allocation concealment, and a large attrition post-randomization. Thus, among 50 patients assigned to autologous HCT, 13 (26%) did not receive the planned treatment (one declined, two had insufficient stem-cell harvest, ten died before treatment) whereas 7 of 50 (14%) assigned to melphalan plus dexamethasone did not receive planned treatment (5 died before treatment, one did not tolerate treatment, one received incorrect treatment). Therefore, even though this was a randomized trial, the results are not sufficient to change the policy statement given the body of evidence available from other, albeit nonrandomized, studies.

Nonrandomized Studies

Several retrospective and prospective series have been reported on the use of autologous HCT in patients with AL. Results from these series are consistent with others that suggest autologous HCT is feasible and beneficial in selected patients with AL.[4-27]

A 2015 report from the Center for International Blood and Marrow Transplant Research Study identified 1536 patients with amyloidosis who had undergone autologous HCT between 1995 and 2012.[28] Early mortality and OS were analyzed in three time cohorts: 1995 to 2000, 2001 to 2001, and 2007 to 2012. Over this time period, OS improved from 55% to 77%, while early mortality decreased from 20% to 5%. Multivariate analysis showed that cardiac involvement was associated with high mortality and inferior OS. Higher dosages of melphalan were associated with a lowered relapse risk.

Parmar (2014) compared autologous HSCT with conventional therapies (CTR) in AL patients over a period of 14 years.[29] Autologous HCT was performed in 80 patients with a one-year non-relapse mortality rate of 12.5%. Novel agents were used as part of induction therapy in 56% of transplant recipients compared with 46% of CTR patients. Outcomes of hematological and organ responses were observed in 74.6% and 39% in the autologous HCT patients compared with 53% and 12% in the CTR patients, respectively. The projected five-year survival for autologous HCT compared with CTR was 63% vs 38%, respectively. Autologous HSCT patients who were alive one year after initial diagnosis experienced improved five-year OS (72%) versus 65% in CTR patients. Multivariate analysis demonstrated that age older than 60 years, induction therapy with novel agents, kidney only involvement and autologous HCT were significantly associated with improved survival. Study authors concluded that autologous HCT was associated with long-term survival in patients with AL amyloidosis.

Section Summary

Available evidence is sufficient to demonstrate a treatment benefit associated with autologous HCT in patients with AL amyloidosis. Data on the use of allogeneic HCT to treat AL amyloidosis are sparse, with no systematic evaluation in a clinical trial.[30] Until clinical trials reporting the use of allogeneic HCT are reported in the scientific literature, the safety and effectiveness of this treatment in primary amyloidosis will remain unknown.

WALDENSTRÖM MACROGLOBULINEMIA

The evidence supporting the use of autologous or allogeneic hematopoietic cell transplantation (HCT) in patients with WM consists of non-randomized trials, several of them with retrospective study designs.

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Sakurai (2020) reported results of a retrospective study of patients with WM treated with SCT. The registry database from the Japan Society for Hematopoietic Cell Transplantation was used to identify 46 patients who received autologous transplantation and 31 who received allogeneic transplantation. More patients with advanced disease status at the time of transplantation were identified in the allogeneic SCT group. Additionally, patients in the allogeneic group received more lines of chemotherapy. The one-year cumulative incidences of NRM were 30.0% (95% CI, 14.7 to 46.9%) in the allogeneic SCT and 0% in the autologous SCT group. The estimated three-year OS and PFS rates were 84.5% (95% CI, 66.0 to 93.4%) and 70.8% (95% CI, 53.0 to 82.9%), respectively, in the autologous SCT group, and 52.2% (95% CI, 32.5 to 68.6%) and 45.0% (95% CI, 26.3 to 62.0%), respectively, in the allogeneic SCT group.

A retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) registry analysis of SCT (autologous, n=10, allogeneic, n=26) for WM reported three-year overall survival rates of 46% (95% CI, 27 to 65%) for allogeneic HSCT recipients and 70% (95% CI, 40 to 93%) for autologous HSCT patients.[31] Although the CIBMTR results appear favorable, it should be noted that patients in this report were heavily pretreated, highly heterogeneous in terms of disease characteristics and risk factors, and received a variety of conditioning regimens, including myeloablative and RIC, between 1986 and 2002.

Kyriakou (2010) reported on 158 adult patients with WM reported to the European Group for Blood and Marrow Transplantation (EBMT) between January 1991 and December 2005.[32] Median time from diagnosis to autologous HSCT was 1.7 years (range, 0.3 to 20.3 years), 32% of the patients had experienced treatment failure with at least three 3 of therapy, and 93% had sensitive disease at the time of transplant. Median follow-up for surviving patients was 4.2 years (range: 0.5 to 14.8 years). Nonrelapse mortality was 3.8% at one year. The estimated five-year relapse rate was 52.1%. Progression-free survival (PFS) and OS were 39.7% and 68.5%, respectively, at five years and were significantly influenced by number of lines of therapy and the degree of chemorefractory at HSCT. The authors conclude that autologous HSCT is a feasible procedure in young patients with advanced WM but that it should not be offered to patients with chemoresistant disease and to those who received more than three lines of therapy.

Kyriakou (2010) also reported on a retrospective analysis of a smaller group of patients who had allogeneic HSCT for WM.[33] A total of 86 patients received allogeneic HSCT by using either myeloablative conditioning (MAC; n=37) or reduced-intensity conditioning (RIC; n=49) regimens. The median age was 49 years (range: 23 to 64 years); 47 patients had received three or more previous lines of therapy, and 8 patients had experienced failure on a prior autologous HSCT. A total of 59 patients (68.6%) had chemotherapy-sensitive disease at the time of allogeneic SCT. Median follow-up of the surviving patients was 50 months. The overall response rate was 75.6%. The relapse rates at three years were 11% for MAC and 25% for RIC. Overall survival at five years was 62% for MAC and 64% for RIC, respectively. The occurrence of chronic graft-versus-host (GVH) disease was associated with a lower relapse rate. The authors concluded that allogeneic HSCT can induce durable remissions in a selected population of young and heavily pretreated patients who have WM.

Cornell (2016) reported retrospectively on 144 adult patients entered in the Center for International Blood and Marrow Transplant Research registry between 2001 and 2013 who underwent allogeneic HCT.[34] Patients had relapsed after receiving at least one line of prior therapy. Hematopoietic cells were obtained from HLA matched or mismatched donors; cord blood stem cells were excluded. A total of 67 patients received myeloablative conditioning and

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67 received reduced intensity conditioning. Over half of patients (n=82 [57%]) had chemosensitive disease. Overall survival (OS) was 74% at one year and 52% at five years. Patients with chemosensitive disease had significantly better one-year and five-year overall survival compared with patients with chemoresistant disease.

Section Summary

As for AL amyloidosis, available data on the use of autologous HCT for WM are sufficient (because of rarity of the disease) to indicate a potential treatment benefit in patients with this rare type of B cell malignancy who have failed other treatment options. Available evidence is not sufficient to indicate whether patients treated with allogeneic HCT experience a similar treatment benefit.

PRACTICE GUIDELINE SUMMARY

AL AMYLOIDOSIS

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for Systemic Light Chain Amyloidosis (v1.2020) which state that primary treatment options include high-dose chemotherapy followed by stem cell transplant.[35]

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT; currently named the American Society for Transplantation and Cellular Therapy) issued guidelines on the indications for autologous and allogeneic hematopoietic cell transplantation (HCT).[36] ASBMT gave the rating of N (not generally recommended; neither evidence nor clinical practice support the routine use) for the use of allogeneic HCT for the treatment of primary amyloidosis in adults. ASBMT gave a rating of C (standard of care; clinical evidence available) for the use of autologous HCT in the treatment of primary amyloidosis in adults.

British Committee for Standards in Haematology

The British Committee for Standards in Haematology convened a working group to develop guidelines on the management of AL amyloidosis, which were published in 2015.[37] Below is a summary of the guidelines on high dose melphalan and autologous stem cell transplantation (HDM-ASCT) and allogeneic transplantation as treatments of AL amyloidosis:

- HDM-ASCT recommended as preferred first line treatment for patients (grade 1c):
    - Up to 65-70 years of age
    - Estimated glomerular filtration rate >50 ml/min
    - Low cardiac biomarkers
    - Low level plasma cell infiltration in bone marrow at time of transplant
    - Without the following contraindications:
        - Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide >590 pmol/l and/or troponin-T >0.06 ng/ml
        - Severe autonomic neuropathy
        - Significant gastrointestinal bleeding
        - Recurrent pleural effusions
        - Eastern Cooperative Oncology Group performance status >2

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- HDM-ASCT may be considered for select patients up to 65-70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy (grade 1c)
- Allogeneic transplantation is generally not recommended due to high treatment-related mortality, but may be considered in relapsed younger patients with limited organ involvement who have a matched sibling donor

WALDENSTRÖM MACROGLOBULINEMIA

National Comprehensive Cancer Network

The NCCN guidelines (v2.2020) indicate that stem cell transplantation for select cases of Waldenström Macroglobulinemia may be appropriate with either high-dose therapy with autologous stem cell rescue or allogenic stem cell transplant (myeloablative or nonmyeloablative).[38] The NCCN guidelines further state that allogenic stem cell transplantation "should ideally be undertaken in the context of a clinical trial."

Eighth International Workshop on Waldenström Macroglobulinemia

In 2016, consensus recommendations from the Eighth International Workshop on Waldenström Macroglobulinemia were published.[39] The panel concluded that autologous hematopoietic cell transplantation (HCT) is a treatment option for high-risk WM patients who are eligible for transplant. They further stated that autologous HCT should be offered at early relapses and is not as beneficial once patients have been exposed to more than 3 lines of therapy or in those with chemotherapy refractory disease. The definition of "chemotherapy refractory disease" is not specified. Regarding allogeneic HCT, they stated that this treatment, "when appropriate, should preferably be considered in the context of clinical trials."

SUMMARY

AL AMYLOIDOSIS

There is enough research to show that autologous hematopoietic cell transplant (HCT) can improve health outcomes in patients with AL amyloidosis. Therefore, use of this procedure may be considered medically necessary.

There is not enough research to show that allogeneic hematopoietic cell transplant (HCT) improves health outcomes form patients with AL amyloidosis. Therefore, allogeneic HCT is considered investigational in patients with AL amyloidosis.

WALDENSTRÖM MACROGLOBULINEMIA

There is enough research to show that autologous hematopoietic cell transplant (HCT) can improve health outcomes for certain patients with Waldenström macroglobulinemia (WM). Current clinical guidelines based on research recommend that this treatment be considered only among patients who have failed previous treatment and whose disease is responsive to chemotherapy. Therefore, the use of autologous HCT as salvage treatment for WM is considered medically necessary in patients with chemosensitive disease.

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There is enough research to show that autologous hematopoietic cell transplant (HCT) does not improve health outcomes for patients with Waldenström macroglobulinemia that is resistant to chemotherapy. Therefore, the use of autologous HCT in these patients is considered not medically necessary.

There is not enough evidence that autologous hematopoietic cell transplant (HCT) can improve health outcomes when used as a first-line treatment for Waldenström macroglobulinemia (WM). Use of this procedure as a primary treatment of WM is therefore considered investigational.

There is not enough research to show that allogeneic hematopoietic cell transplant (HCT) can improve health outcomes for people with Waldenström macroglobulinemia (WM). Clinical guidelines based on research do not recommend the use of this type of transplantation outside of clinical trials. Therefore, use of allogeneic HCT for treatment of WM is considered investigational.

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41. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis." Policy No. 8.01.42

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*

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Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Utilization Management, Policy No. 13

Air Ambulance Transport

Effective: May 1, 2020

Next Review: February 2021
Last Review: March 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Air ambulance transportation is provided by helicopters (rotary wing) or fixed wing aircraft that are specially designed, equipped, and staffed for transporting sick and injured patients.

MEDICAL POLICY CRITERIA

Note: This policy only applies to member contracts that are subject to preauthorization for air ambulance services, as specified by their group plan. Please check the preauthorization website for the member contract to confirm requirements.

I. Air ambulance transport may be considered **medically necessary** when all of the following criteria (A-C) are met:
   A. Urgent and rapid ambulance transport is essential to stabilize or preserve the patient's life.
   B. One of the following criteria is met:
      1. Transport cannot be safely provided by ground ambulance due to great distances, prolonged transport time, or other obstacles that would endanger the patient's health or threaten survival; or
      2. The point of pick up is inaccessible by ground ambulance.

October 1, 2020

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LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Documentation that the member's medical condition required immediate and rapid ambulance transportation that could not have been provided by ground ambulance.
- Location of transport pick-up.
- Location of transport drop-off.
- Level of care of facility which the member is being transferred to.
- Level of care of facility which the member is being transferred from.
- All additional documentation supporting the need for air ambulance services (i.e., accessibility of the point of pick-up, distances, obstacles, etc.).

CROSS REFERENCES

None

CODES

Codes	Number	Description
CPT	None	
HCPCS	A0140	Nonemergency transportation and air travel (private or commercial) intra- or interstate
	A0430	Ambulance service, conventional air services, transport, one way (fixed wing)
	A0431	Ambulance service, conventional air services, transport, one way (rotary wing)
	A0435	Fixed wing air mileage, per statute mile
	A0436	Rotary wing air mileage, per statute mile
	S9960	Ambulance service, conventional air services, nonemergency transport, one way (fixed wing)

Date of Origin: *March 2013*

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