Transforming Healthcare with Evidence

Update Literature Search
2015 WA HTA on Novocure (Tumor Treating Fields)
Prepared by Winifred S. Hayes, Inc., DBA Hayes, Inc. Under Contract with the
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OVERVIEW

This update literature search provides a basis for deciding whether to update the 2015 Washington HTA on *Novocure (Tumor Treating Fields)* prepared by Hayes, Inc. in 2015.

The following objectives reflect methods guidance for systematic review updates published by the Agency for Healthcare Research and Quality (AHRQ) (Tsertsvadze et al., 2011). They are accompanied by key findings.

Objectives

- Estimate the volume of new literature published since 2015, relative to each component of Key Questions 1 through 3, and using the same general inclusion criteria that were specified for the 2015 report.

  Findings:

  - 1 new systematic review, 2 small case series, and 1 post hoc analysis of Stupp et al. (2015) for KQ1a (effectiveness of Novocure for treatment of glioblastoma)
  - 0 new studies found for KQ1b (effectiveness of Novocure for treatment of other cancers)
  - 1 small case series and 1 post hoc analysis for KQ2 (harms associated with Novocure)
  - 0 new studies found for KQ3 (differential effectiveness of Novocure according to clinical history and patient characteristics)

- Assess whether new evidence fills gaps in the evidence available as of 2015.

  Findings:

  - There is accumulating evidence regarding effectiveness of Novocure for treatment of glioblastoma for increasing overall survival/progression-free survival. However, these studies do not appear to be of sufficient size or design to fill gaps identified in the 2015 report regarding the safety and efficacy of Novocure in patients with glioblastoma and other cancers compared with chemotherapy or other treatment.
  - There is no new evidence designed to systematically investigate differential effectiveness and safety according to patient characteristics and previous treatment history.
  - There were no new studies found investigating the impact of Novocure on quality of life and functional status.

- Assess whether Novocure (tumor treating fields) has been studied in subpopulations or in comparison with specific alternative treatments that were not addressed as of 2015.

- A review of abstracts identified one case series describing the use of Novocure in pediatric patients with glioblastoma
- No new studies assessing new comparators with Novocure were found

- Assess whether new evidence allows stronger conclusions or is likely to modify conclusions, including estimates of the magnitude of benefit.

  Findings:

  - 1 systematic review, 2 small case series, and 1 post hoc analysis adds to the low-quality evidence available for effectiveness of Novocure for treatment of recurrent glioblastoma. Based on a review of abstracts reporting this new evidence, as well as the conclusions being consistent with those found in the 2015 report, the new evidence does not appear to allow stronger conclusions nor is likely to modify conclusions of the 2015 report regarding efficacy of Novocure for recurrent glioblastoma.
  - 1 systematic review and 1 small case series included newly diagnosed glioblastoma patients. This new evidence does not appear to allow stronger conclusions nor is likely to modify conclusions of the 2015 report regarding efficacy of Novocure for newly diagnosed glioblastoma.

Other Comments

- No in-depth search for new harms data, e.g., review of Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) reports or recently published narrative reviews was made.
- No search for new cost or cost-effectiveness data was made.
- No search for new FDA clearances was made.

Changes in CMS Policy

No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified for Novocure/Optune.

Updated Practice Guidelines

One updated practice guideline prepared by the National Comprehensive Cancer Network (NCCN) was identified. The abstract indicates that the panel assessed new data regarding the use of alternating electric field therapy for high-grade gliomas. The new data includes evidence presented in the 2015 report (Mrugala et al., 2014) and 2 abstracts from the EF-14 trial that did not meet inclusion criteria for the 2015 report or this update literature search. The guidelines state, "Based on the 2015 panel vote, the inclusion of 'Consider alternating electric field therapy for glioblastoma' changed from a category 3 to a category 2B recommendation (see GLIO-4, page 1195). The panel awaits peer-reviewed publication of results from the EF-14 trial before deciding whether to add TTF as a treatment option for newly diagnosed glioblastoma" (Nabors et al., 2015).

Ongoing Clinical Trials

The following relevant open studies were identified:

- Effect of TTFields (150 kHz) in Non-small Cell Lung Cancer (NSCLC) Patients With 1-10 Brain Metastases Following Radiosurgery (METIS) (NCT02831959)
- Effect of Tumor Treating Fields (TTFields) (150 kHz) as Second Line Treatment of Non-small Cell Lung Cancer (NSCLC) in Combination With PD-1 Inhibitors or Docetaxel (LUNAR) (NCT02973789)
- TTFields and Pulsed Bevacizumab for Recurrent Glioblastoma (NCT02663271)
- Optune(NOVOTTF-100A)+ Bevacizumab+ Hypofractionated Stereotactic Irradiation Bevacizumab-Naive Recurrent Glioblastoma (GCC 1344) (NCT01925573)
- HUMC 1612: Optune NovoTTF-200A System (NCT03128047)
- Enhancing Optune Therapy With Targeted Craniectomy (NCT02893137)
- Optune Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma (NCT02743078)
- A Phase II Study of NovoTTF-200A Alone and With Temozolomide in Patients With Low-Grade Gliomas (NCT02507232)
- A Phase II Study of Optune (NovoTTF) in Combination With Bevacizumab (BEV) and Temozolomide (TMZ) in Patients With Newly Diagnosed Unresectable Glioblastoma (GBM) (NCT02343549)
- Optune Delivered Electric Field Therapy and Bevacizumab in Treating Patients With Recurrent or Progressive Grade 2 or 3 Meningioma (NCT02847559)
- NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma (NCT01894061)
- Feasibility Trial of Optune for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma (NCT03033992)

See Table 1 on next page for more detail and commentary by Key Question.

References

Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100ATM system for glioblastoma: the Patient Registry Dataset (PRiDe). *Semin Oncol*. 2014;41(Suppl 6):S4-S13.

Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA*. 2015;314(23):2535-2543.

Tsertsvadze A, Maglione M, Chou R, et al. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1208-1215.

Table 1. Summary of New Literature

Key: GBM, glioblastoma; grp, group; HR, hazard ratio; N/A, not applicable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; pts, patients; tx, treatment

Number of Studies and Conclusions from 2015 Report	New Systematic Reviews/ Technology Assessments	Primary Studies Published 2015 or Later	Potential Impact of New Evidence
KQ1a. What is the clinical effectiveness of Novocure for tx of GBM?			
5 studies (n=873) for recurrent GBM **Overall quality: Low** **Findings:** Studies consistently demonstrated that Novocure was comparable w/ chemotherapy alone w/ some inconsistency for OS and PFS on whether Novocure was more effective than chemotherapy alone. 2 studies (n=325) for newly diagnosed GBM **Overall quality: Very low** **Findings:** Novocure was more effective than chemotherapy.	1 systematic review Mittal et al. (2017): Narrative review of Novocure trials that were analyzed in the 2015 report, separated by studies assessing newly diagnosed vs recurrent GBM. Conclusions are consistent w/ those of the 2015 report.	Ansstas and Tran (2016): Case series (n=8), recurrent GBM, median OS following Novocure tx was 216 days (7.2 mos). Green et al. (2017): Case series (n=5 children), recurrent GBM (n=3) and newly diagnosed GBM (n=2; 60% of pts showed partial response to Novocure tx). Kesari and Ram (2017): Post hoc analysis of Stupp et al. (2015) (n=695), recurrent GBM, compared Novocure plus chemotherapy w/ chemotherapy alone after first GBM recurrence. Median OS in the Novocure plus chemotherapy grp was significantly longer versus chemotherapy alone (11.8 vs 9.2 mos; HR, 0.70; 95% CI, 0.48-1.00; *P*=0.049).	1 systematic review, 2 small case series, and 1 post hoc analysis adds to the low-quality evidence available for effectiveness of Novocure for tx of recurrent GBM. Findings of the systematic review were consistent w/ those of the 2015 report. Only 1 study (Kesari and Ram) compared Novocure plus chemotherapy w/ chemotherapy alone, and the results were consistent with the 2015 report. Based on a review of abstracts reporting this new evidence, as well as the conclusions being consistent w/ those found in the 2015 report, the new evidence does not appear to allow stronger conclusions nor is likely to modify conclusions of the 2015 report regarding efficacy of Novocure for recurrent GBM. 1 systematic review and 1 small case series included newly diagnosed GBM

Number of Studies and Conclusions from 2015 Report	New Systematic Reviews/ Technology Assessments	Primary Studies Published 2015 or Later	Potential Impact of New Evidence
			pts. This new evidence does not appear to allow stronger conclusions nor is likely to modify conclusions of the 2015 report regarding efficacy of Novocure for newly diagnosed GBM. The case series by Green et al. (2017) is a feasibility study in 5 children, which is a new subpopulation, but it is unlikely to impact the conclusions of the 2015 report.
KQ1b. What is the clinical effectiveness of Novocure for tx of other cancers?			
NSCLC: 1 study (n=41) **Overall quality:** Very low **Findings:** No comparison grp; 15% of NSCLC pts exhibited a partial response to Novocure tx. Solid tumors from breast cancer, melanoma, and mesothelioma: 1 study (n=6) **Overall quality:** Very low **Findings:** No comparison grp; 17% of solid tumor pts exhibited a partial response to Novocure tx	No systematic reviews found	No primary studies found.	N/A

Number of Studies and Conclusions from 2015 Report	New Systematic Reviews/ Technology Assessments	Primary Studies Published 2015 or Later	Potential Impact of New Evidence
KQ2. What are the harms associated with Novocure?			
Overall quality: Low 8 studies **Findings:** No serious adverse events related to Novocure tx were reported. The most common complication reported was mild to moderate dermatitis under the transducer arrays (16% to 90%). 2 studies reported 1% to 7% of pts experienced skin ulcers.	No systematic reviews found	Green et al. (2017): Case series (n=5 children), recurrent GBM and newly diagnosed GBM, all pts tolerated Novocure without tx-limiting toxicities. Kesari and Ram (2017): Post hoc analysis of Stupp et al. (2015) (n=695), newly diagnosed GBM, compared Novocure plus chemotherapy w/ chemotherapy alone after first GBM recurrence. Novocure showed a low toxicity safety profile w/ no grade 3/4 device-related adverse event.	1 small case series and 1 post-hoc analysis adds to the low-quality evidence available for safety of Novocure for tx of recurrent GBM. Consistent with the 2015 report, no serious adverse events were reported with Novocure tx. Based on a review of abstracts reporting this new evidence, as well as the conclusions being consistent with those found in the 2015 report, the new evidence does not appear to allow stronger conclusions nor is likely to modify conclusions of the 2015 report regarding safety of Novocure for GBM.
KQ3. Does the effectiveness of Novocure or incidence of adverse events vary by clinical history or patient characteristics?			
Overall quality: Very low **Findings:** Median OS and PFS were longer in studies that enrolled a higher number of pts w/ fewer prior episodes of GBM (6 studies). Pts that required lower daily doses of dexamethasone exhibited longer OS (1 study).	No systematic reviews found	No primary studies found.	N/A

Number of Studies and Conclusions from 2015 Report	New Systematic Reviews/ Technology Assessments	Primary Studies Published 2015 or Later	Potential Impact of New Evidence
Pts w/ a more favorable functional score had significantly longer OS (2 studies). Pts not exposed to bevacizumab tx prior to Novocure tx were more likely to respond to tx (2 studies). Pts w/ secondary GBM upgraded from low-grade gliomas were more likely to respond to tx (1 study). Pts w/ a smaller tumor size were more likely to respond to tx (1 study). Pts that were compliant w/ using their Novocure device had longer OS (3 studies).			

METHODS

Systematic Search (Task A1): Key Systematic Reviews, Technology Assessments, and Practice Guidelines

1. The following databases were searched on May 4, 2017, and again on May 20, 2017, using the terms *Novocure or Optune or NovoTTF or "tumor treating fields" or "tumor treatment fields" or TTfield or TTfields or "alternating electric field" and* limiting searches to publication in September 2015 or later:

    a. PubMed, using filters for systematic review (SR), meta-analysis, and practice guideline

    b. Centre for Reviews and Dissemination (CRD)

    c. Cochrane Library

    d. AHRQ

2. Select relevant publications.

Systematic Search (Task A2): Literature Review

2. Searched PubMed and Embase, September 2015 to May 2017, to identify new publications to answer Key Questions 1, 2, and 3.

    a. Search terms combined using "OR":

        1. Novocure
        2. Optune
        3. NovoTTF
        4. "Tumor treating fields"
        5. "Tumor treatment fields"
        6. TTfield
        7. TTfields
        8. "Alternating electric field"

    b. Limited to English language and studies of humans (as in 2015 report).

    c. Excluded publications if they: contained no quantitative data for assessing impact of Novocure treatment; were conference abstracts; were case studies or series of case reports (as in 2015 report).

3. Conducted 1 final PubMed and Embase search before submitting final update literature search document, going back 6 months and without filters, to assure no recently added publications are missed.
4. Searched for relevant CMS NCDs using the keywords novocure or tumor or glioblastoma or field.
5. Searched ClinicalTrials.gov for open studies using keywords Novocure or TTFields to identify any relevant in-progress research.

Summary of the Volume of New Studies, by Key Question (Task B)

A summary table was created providing information on the following:

- Numerical search results (number of trials, systematic reviews, technology assessments, nonrandomized trials, case series, and registry studies)
- Tabulated by Key Question.

Assessment of the Impact on Conclusions (Task C)

The following information was added to the above summary table.

1. Comments about potential impact of new publications on conclusions for each Key Question. Based on information in publication abstracts and/or executive summaries and key tables of systematic reviews and technology assessments. Comments were based on a consideration of the factors listed under **Objectives**.

2. Conclusions of new systematic reviews and technology assessments added to summary table. Assess level of controversy by comparing conclusions across reports.

Appendix I. Bibliography

The bibliography is listed in alphabetical order.

SYSTEMATIC REVIEW

Mittal S, Klinger NV, Michelhaugh SK, Barger GR, Pannullo SC, Juhasz C.
Alternating electric tumor treating fields for treatment of glioblastoma: Rationale, preclinical, and clinical studies. *Journal of neurosurgery.* 2017:1-8.

OBJECTIVE Treatment for glioblastoma (GBM) remains largely unsuccessful, even with aggressive combined treatment via surgery, radiotherapy, and chemotherapy. Tumor treating fields (TTFs) are low-intensity, intermediate-frequency, alternating electric fields that have antiproliferative properties in vitro and in vivo. The authors provide an up-to-date review of the mechanism of action as well as preclinical and clinical data on TTFs. METHODS A systematic review of the literature was performed using the terms "tumor treating fields," "alternating electric fields," "glioblastoma," "Optune," "NovoTTF-100A," and "Novocure." RESULTS Preclinical and clinical data have demonstrated the potential efficacy of TTFs for treatment of GBM, leading to several pilot studies, clinical trials, and, in 2011, FDA approval for its use as salvage therapy for recurrent GBM and, in 2015, approval for newly diagnosed GBM. CONCLUSIONS Current evidence supports the use of TTFs as an efficacious, antimitotic treatment with minimal toxicity in patients with newly diagnosed and recurrent GBM. Additional studies are needed to further optimize patient selection, determine cost-effectiveness, and assess the full impact on quality of life.

PRIMARY STUDIES

Ansstas G, Tran DD.
Treatment with tumor-treating fields therapy and pulse dose bevacizumab in patients with bevacizumab-refractory recurrent glioblastoma: A case series. Case Reports in Neurology. 2016;8(1):1-9.

Patients with bevacizumab-refractory recurrent glioblastoma multiforme (GBM) have a poor prognosis. We propose that instead of continuing on bevacizumab, patients should switch to treatment with Optune™, a novel antimitotic Tumor-Treating Fields (TTFields) therapy approved in the United States for newly diagnosed and recurrent GBM. This would reserve bevacizumab for subsequent disease progression. In this case series, we describe 8 patients with recurrent GBM who had disease progression on bevacizumab, discontinued bevacizumab treatment, and were treated with TTFields therapy alone. After subsequent radiographic or clinical progression, 5 patients were rechallenged with bevacizumab in a 'pulse dose' fashion, an approach not previously described. Following treatment with TTFields therapy, median overall survival (OS) was 216 days (7.2 months). Median OS from last dose of initial bevacizumab was 237 days (7.9 months), twice that of historical controls for bevacizumab failures, and median OS from the first dose of bevacizumab rechallenge was 172 days (5.7 months). TTFields therapy was well tolerated, with a mean adherence rate of 74.2% (range, 48.2-92.9%). These results support the use of TTFields therapy with pulse dose bevacizumab as an option in patients with refractory GBM.

Green AL, Mulcahy Levy JM, Vibhakar R, et al.
Tumor treating fields in pediatric high-grade glioma. Child's Nervous System. 2017:1-3.

Purpose: Tumor treating fields (TTF) are alternating electric fields applied continuously to the scalp. The treatment is approved for both primary and recurrent supratentorial adult glioblastoma but unstudied in children. Methods: We report a feasibility case series of five pediatric high-grade glioma patients (ages 10–20 years) treated at our institution with TTF along with chemotherapy and/or radiation. Results: Two patients began therapy at second recurrence and showed progressive disease. Two others were treated upfront after radiation therapy, and both showed partial responses. A fifth patient was treated at first recurrence and also showed a partial response. All five tolerated TTF well without treatment-limiting toxicities. Conclusions: The tolerability of TTF, combined with the adult data, justify a pediatric clinical trial.

Kesari S, Ram Z.
Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: A post hoc analysis of the ef-14 trial. CNS Oncology. Epub April 12, 2017.

BACKGROUND: This post hoc analysis of the EF-14 trial (NCT00916409) of tumor-treating fields (TTFields) plus temozolomide versus temozolomide alone in newly diagnosed glioblastoma compared the efficacy of TTFields plus chemotherapy (physician's choice) versus chemotherapy alone after first recurrence. METHODS: Patients on TTFields plus temozolomide continued TTFields plus second-line chemotherapy after first recurrence. Some patients on temozolomide alone crossed over after approval of TTFields for recurrent GBM. The primary efficacy outcome was overall survival (OS). RESULTS: After disease progression, 131 patients received TTFields plus chemotherapy and 73 chemotherapy alone. Thirteen patients in the original temozolomide-alone group crossed over to receive TTFields plus chemotherapy after disease progression, resulting in 144 patients receiving TTFields plus chemotherapy and 60 chemotherapy alone. Median follow-up was 12.6 months. Bevacizumab, alone or with cytotoxic chemotherapy, was the most frequent treatment. Median OS in the TTFields plus chemotherapy group was significantly longer versus chemotherapy alone (11.8 vs 9.2 months; HR: 0.70; 95% CI, 0.48-1.00; p=0.049). TTFields showed a low toxicity safety profile, as previously reported, with no grade 3/4 device-related adverse events. CONCLUSION: TTFields plus chemotherapy after first disease recurrence on TTFields plus temozolomide or temozolomide alone prolonged OS in patients in the EF-14 trial.

UPDATED GUIDELINE

Nabors LB, Portnow J, Ammirati M, et al.

Central nervous system cancers, version 1.2015. J Natl Compr Canc Netw. 2015;13(10):1191-1202.
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System (CNS) Cancers provide interdisciplinary recommendations for managing adult CNS cancers. Primary and metastatic brain tumors are a heterogeneous group of neoplasms with varied outcomes and management strategies. These NCCN Guidelines Insights summarize the NCCN CNS Cancers Panel's discussion and highlight notable changes in the 2015 update. This article outlines the data and provides insight into panel decisions regarding adjuvant radiation and chemotherapy treatment options for high-risk newly diagnosed low-grade gliomas and glioblastomas. Additionally, it describes the panel's assessment of new data and the ongoing debate regarding the use of alternating electric field therapy for high-grade gliomas.