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DERP VI Update Scan 8:

Newer Antiemetics

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OHSU

Drug Effectiveness Review Project

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Objectives

The purpose of this literature scan is to preview the amount and nature of new research that has emerged since the last full review on newer antiemetics for nausea and vomiting associated with surgical procedures, chemotherapeutic agents, radiation therapy, and pregnancy. The literature search for this scan focuses on new randomized controlled trials (RCTs) and systematic reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last update report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participating organizations agreed to proceed with a full report update or other review product.

Topic History

Expanded Scan 7: February 2017

Scan 6: July 2016

Scan 5: July 2015

Scan 4: May 2014

Scan 3: April 2013

Scan 2: March 2011

Scan 1: December 2009

Update 1: January 2009, searches through October 2008

Background and Context

Nausea and vomiting are major concerns for patients undergoing chemotherapy and radiation therapy,[1,2] and are frequently associated with surgical procedures; the estimated incidence is around 25% to 30%.[3] Nausea and vomiting also commonly occur during pregnancy: prevalence rates are between 50% and 80% for nausea and 50% for vomiting and retching.[4,5] The most severe and persistent form of pregnancy-related nausea and vomiting, hyperemesis gravidarum, can lead to serious complications, including dehydration, metabolic disturbances, nutritional deficits requiring hospitalization, and death.[6]

Key Questions

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?
2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?

3. Are there subgroups of patients based on demographics (e.g., age, race, and gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Using the PICO outlined below, we screened our search results for eligible systematic reviews, meta-analyses, and RCTs published since the implementation of the search in the most recent scan, which occurred in January 2017.

Populations

Adults or children at risk for or with nausea, vomiting (including retching), or both, related to the following therapies and conditions:

- Radiation therapy
- Surgical procedure
- Pregnancy
- Chemotherapy of varying emetogenicity (The last update report used the emetogenicity classification scale for chemotherapy regimens that Hesketh defined in 1997 and modified in 1999.[7,8] Chemotherapeutic agents rated 1 have a low emetic potential; agents rated 5 are severely emetic (>90% chance of emesis).

Interventions

Table 1. Included Interventions

Generic Name	Brand Name(s)	Route of Administration
Aprepitant	Emend	Oral
Dolasetron	Anzemet	Injectable, oral
Doxylamine Succinate/Pyridoxine Hydrochloride	Diclegis Bonjesta	Tablet, oral, delayed release
Fosaprepitant	Emend	Injectable
Granisetron	Kytril Sancuso Sustol	Injectable, oral, transdermal patch
Netupitant/Palonosetron	Akynzeo	Capsule, oral
Ondansetron	Zofran Zuplenz	Injectable, oral, orally disintegrating tablet, oral film
Palonosetron	Aloxi	Injectable
Rolapitant	Varubi	Tablets, oral

Comparators

- Any active, FDA-approved comparator
- No treatment
- Placebo

We focused on head-to-head evidence for newer antiemetics. Where there was limited or no evidence from head-to-head trials, we included active- or placebo-controlled trials.

Outcomes

- Defined differently by indication, including
  - Success at different times (early or late/delayed)
  - Satisfaction
  - Quality of life
  - Need for rescue medications
  - Number of episodes of emetic events
  - Degree of nausea
  - Serious events related to any emetic event
  - Delay until first emetic event
  - Number of emesis-free days
  - Worst day of nausea/vomiting
  - Duration of hospitalization

Methods

We searched the FDA website to identify newly approved drugs and indications, any first generic approvals, and new serious harms (e.g., boxed warnings) for included interventions. To identify new drugs, we also searched CenterWatch, a privately owned database of clinical trials information. To identify relevant literature, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2017 to May 2018, using terms for included drugs and limits for English language and humans. We also conducted an internet search using Google and Google Scholar with key words for included drugs.

Findings

New Drugs or Formulations

Since the search was conducted in the last update report in January 2009, 11 new antiemetic drugs and formulations (Table 2) have been approved by the FDA.[9] Since scan 7 in February 2017,[10] 1 first generic and 3 new formulations were approved.

Table 2. Newly Approved Antiemetic Drugs, First Approved Generics, and Formulations Since the Update Report[11]

Generic Name	Brand Name	Date of FDA Approval	Drug Class	Formulation	Indication(s)
Ondansetron	Zuplenz	July 2010	5-HT3 antagonist	Oral film	Prevention of nausea and vomiting associated with MEC and HEC Prevention of nausea and vomiting associated with radiotherapy of the abdomen Prevention of postoperative nausea and/or vomiting
Granisetron	Sancuso	September 2011	5-HT3 antagonist	Transdermal patch	Prevention of nausea and vomiting associated with MEC and HEC
Doxylamine Succinate 10mg/ Pyridoxine Hydrochloride 10mg (FDCP)	Diclegis	April 2013	Other	Delayed release tablet	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
Netupitant/ Palonosetron (FDCP)	Akynzeo	October 2014	NK1/ 5-HT3 antagonist	Capsule	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to HEC
Rolapitant	Varubi	September 2015	NK1 antagonist	Tablet	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to HEC
Granisetron	Sustol	September 2016	5-HT3 antagonist	Subcutaneous injection, extended release	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens

Doxylamine Succinate 20mg/ Pyridoxine Hydrochloride 20mg (FDCP)	Bonjesta	November 2016	Other	Delayed release tablet	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
Doxylamine Succinate 10mg/ Pyridoxine Hydrochloride 10mg (FDCP)		June 2017 *First approved generic product	Other	Delayed release tablet	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
Rolapitant	Varubi	October 2017	NK1 antagonist	IV infusion	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to HEC
Aprepitant	Cinvanti	November 2017	Substance P/NK1 antagonist	IV infusion	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and delayed nausea and vomiting associated with initial and repeat courses of MEC
Netupitant/ Palonosetron (FDCP)	Akynzeo	April 2018	NK1/ 5-HT3 antagonist	IV infusion	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC In combination with dexamethasone

Abbreviations. FDA: Food and Drug Administration; FDCP: fixed-dose combination product; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy.

New Indications

Since the last scan in February 2017, the FDA amended the prescribing information for fosaprepitant IV injection to include the following:

- A defined age range for pediatric use (April 2018)
  - Emend for injection, in combination with other antiemetic agents, is indicated in adults and pediatric patients 6 months of age and older[12]
- Recommended dose regimens for pediatric use of the injectable and oral formulations (April 2018)
  - By type of chemotherapy regimen (single day or multiday)[12]
  - By age and weight of the patient[12]
- Instructions for the preparation of the injectable formulation (April 2018)[12]
- Information on hypersensitivity reactions (August 2017)
  - Symptoms[12]
  - Monitoring and discontinuation advice[12]
- Information on infusion site reactions (April 2018)
  - Types and timing of reactions[12]
  - Infusion administration and discontinuation advice[12]

The FDA also amended the prescribing information for rolapitant IV injection and oral use in October 2017 to include the following:

- Information on the dosage regimen for both formulations for highly and moderately emetogenic chemotherapy therapies[13]
- Instructions for administration of the injectable emulsion[13]
- Contraindications[13]
- Interactions with CYP2D6 substrates[13]

The FDA also updated the prescribing information in 2017 for granisetron transdermal patch (Sancuso)[14] and palonosetron for IV infusion,[15] but the specific sections were not annotated.

New Serious Harms

In January 2018, the manufacturer of Varubi (rolapitant) issued an important drug warning to health care providers.[16] Postmarketing reports of anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions associated with the use of rolapitant injectable emulsion were highlighted in the warning.[16] The reactions occurred during or soon after the infusion of rolapitant injectable emulsion, and most reactions occurred within the first few minutes of administration.[16] Some of the reactions required hospitalization.[16]

The warning letter issued advice on actions if anaphylaxis or any other serious hypersensitivity/infusion reaction occurred.[16]

- Stop administration of rolapitant injectable emulsion immediately
- Initiate appropriate medical management (including epinephrine and or antihistamines)

- Permanently discontinue rolapitant injectable emulsion

The FDA updated the prescribing information for rolapitant in March 2018 to reflect concern about anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions.[17]

Systematic Reviews

Since the last update report on this topic,[9] we have identified 4 systematic reviews on the efficacy and safety of the newer antiemetics.[18-21]

- A rapid review on the effectiveness and safety of ondansetron for chemotherapy-induced nausea and vomiting (CINV) in children[18]
- A rapid review on the effectiveness and safety of long-term use (> 5 days) of ondansetron, dolasetron, and granisetron for the prevention of nausea and vomiting[19]
- A Cochrane review on the management of pregnancy-related nausea and vomiting[20]
- A Cochrane review on antiemetic medication for the prevention and treatment of (CINV) in children[21]

We did not identify any new systematic reviews in this scan. We identified 1 Cochrane review on drugs for postoperative nausea and vomiting that was withdrawn in 2017.[22] The original review was published in 2002,[23] with an update in 2006.[24] The 2006 review evaluated over 60 antiemetic drugs and included 737 studies involving 103,237 people.[24] In 2017, the review was withdrawn because, at the time of writing, 67 of the included 737 studies had been retracted and investigations were underway for other studies.[22] The original DERP report on antiemetics[25] included 5 publications from the studies under investigation,[26-30] 4 of which are now retracted.[27-30]

Randomized Controlled Trials

Since the last update report on this topic,[9] we have identified 76 relevant trials[31-107]:

- 34 head-to-head trials[53-86]
- 22 trials comparing the addition of an NK1 antagonist to standard therapy[31-52]
- 20 placebo-controlled trials[87-107]

Of these, we identified 5 new trials in this scan (Table 3).[31,32,40,49,74]

Table 3. Characteristics of New Trials

Author, Year NCT Number	Population	Intervention	Comparator	Outcomes
Head-to-head comparisons				
Nakagaki et al., 2017[74] Not reported	40 adults undergoing HSCT	Palonosetron IV	Ondansetron IV	Composite outcome of no emesis, no use of rescue medication, and reduction in nausea Reduction in nausea Adverse events
Addition of an NK1 antagonist (with or without dexamethasone)				
Aapro et al., 2017[31] NCT01339260	1,455 adults with a solid malignant tumor undergoing HEC[a]	Netupitant/ palonosetron	Palonosetron	Complete response Incidence of emesis Incidence of significant nausea Complete protection Quality of life Cardiac safety Adverse events Withdrawals due to adverse events
Abdel-Malek et al., 2017[32] Not reported	15 adults with diffuse large B cell lymphoma undergoing HEC	Aprepitant + ondansetron	Ondansetron	Complete response Incidence of nausea Duration of nausea Incidence of vomiting Patient preference
Kim et al., 2017 NCT01636947[40]	494 adults with a broad range of tumor types undergoing MEC	Aprepitant + ondansetron IV	Ondansetron IV	Incidence of vomiting Complete response Adverse events Withdrawals due to adverse events
Song et al., 2017[49] Not reported	108 adults with B- or T-cell non-Hodgkin lymphoma undergoing HEC	Aprepitant + ondansetron IV	Ondansetron IV	Complete response Incidence of emesis Incidence of nausea Complete protection Quality of life Cardiac safety Adverse events Withdrawals due to adverse events

Abbreviations. HEC: highly emetogenic chemotherapy; HSCT: hematopoietic stem cell transplantation; MEC: moderately emetogenic chemotherapy. Note. [a]The chemotherapy regimen was classified as being moderately emetogenic in 2014. In the 2017 report, the authors reclassified the chemotherapy regime as highly emetogenic because it is commonly administered to young women with breast cancer, a group in which the emetogenic risk is substantially increased because of additional patient-related risk factors.

Since the last update report on this topic,[9] we have identified 7 secondary analyses[108-114]:

- 4 subgroup analyses of published trials[111-114]
- 3 pooled analyses of published trials[108-110]

Of these, we identified 4 new secondary analyses in this scan (Table 4).[108,109,111,114]

Table 4. Characteristics of New Secondary Analyses

Author, Year	Study Description	Population	Intervention	Comparator	Outcomes
Aapro et al., 2017[111]	Retrospective analysis of 1 randomized phase 2 trial and 2 randomized phase 3 trials	Older patients undergoing MEC or HEC	Netupitant/ palonosetron	Palonosetron	Complete control Complete response Adverse events Cardiac safety
Rugo et al., 2017[114]	Post hoc analysis of 2 randomized phase 3 trials	Patients with breast cancer undergoing MEC or HEC	Netupitant/ palonosetron	Palonosetron or Aprepitant + palonosetron	Complete response No significant nausea Quality of life
Barbour et al., 2017[108]	Integrated safety analysis of 4 double-blind, randomized phase 2 or 3 studies	Patients undergoing MEC or HEC	Rolapitant + 5-HT3 antagonist + dexamethasone	5-HT3 antagonist + dexamethasone	Treatment-emergent adverse events Serious treatment-emergent adverse events
Chasen et al., 2017[109]	Pooled post hoc analysis of 2 RCTs and a prespecified analysis of 1 RCT	Patients undergoing MEC or HEC	Rolapitant + 5-HT3 antagonist + dexamethasone	5-HT3 antagonist + dexamethasone	FLIE total score Nausea and vomiting domain scores Impact on daily life

Abbreviations. FLIE: Functional Living Index-Emesis; HEC: highly emetogenic chemotherapy; HSCT: hematopoietic stem cell transplantation; MEC: moderately emetogenic chemotherapy.

Summary

- We identified 3 newly approved drugs for nausea and vomiting associated with surgical procedures, chemotherapeutic agents, radiation therapy, and pregnancy since the last update report. No newly approved drugs were identified in this scan.
- We identified 8 new formulations or first generic approvals since the last update report, of which 4 are new in this scan:
  - 1 first generic approval for doxylamine succinate 10mg/ pyridoxine hydrochloride 10mg delayed release tablets
  - 3 new formulations of aprepitant, netupitant/palonosetron, and rolapitant (IV infusion)
- We identified new prescribing information in this scan on the use of fosaprepitant IV:
  - A defined age range for pediatric use
  - Recommended dose regimens for children
  - How to identify and manage hypersensitivity and infusion site reactions
- We identified new prescribing information in this scan on the use of rolapitant (IV and oral):
  - Dose regimens
  - Contraindications and interactions
- We identified a new serious harm in this scan for rolapitant:
  - Anaphylaxis, anaphylactic, shock and other serious hypersensitivity reactions associated with the use of rolapitant injectable emulsion
- We identified 4 systematic reviews since the last update report. No new systematic reviews were identified in this scan.
- We identified 76 new trials since the last update report, of which 5 are new in this scan:
  - 1 head-to-head trial comparing palonosetron IV and ondansetron IV in adults undergoing hematopoietic stem cell transplantation
  - 4 add-on trials in adults undergoing chemotherapy, comparing the addition of an NK1 antagonist (aprepitant or netupitant) to a 5-HT3 antagonist (palonosetron or ondansetron), with or without dexamethasone
- We identified 20 placebo-controlled trials since the last update report. No new placebo-controlled trials were identified in this scan.
- We identified 7 secondary analyses of published RCTs, of which 4 were identified in this scan:
  - 2 pooled analyses
  - 2 subgroup analyses (older patients and patients with breast cancer)

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Appendix A. Abstracts of Relevant Randomized Controlled Trials

New studies are highlighted in gray.

Head-to-Head Trials

Basu A, Saha D, Hembrom BP, Roy A, Naaz A. Comparison of palanosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. *J Indian Med Assoc*. 2011;109(5):327-329.

The objective of the study was to compare the efficacy of palanosetron (0.25 mg), granisetron (3.0 mg) and ondansetron (8.0 mg) used as anti-emetics for the prevention of postoperative nausea/vomiting in patients undergoing middle ear surgery. The study was done among 75 adult patients (age group 30-45 years) of which 50 were males and rest (25) females, all of ASA I and ASA II. The patients were randomly allocated into 3 equal groups: Group I (n = 25) received injection palanosetron (0.25 mg) IV, group II (n = 25) received injection granisetron (3 mg) IV and group III (n = 25) received injection ondansetron (8.0 mg) IV at the end of the surgical procedure. A standard general anaesthesia technique was employed. Emetic episodes and safety assessments were performed during two periods of 0-6 hours in the postanaesthesia care unit and 6-24 hours in the ward after anaesthesia. The incidence of emesis-free patients during the 0-6 hours period was 100% for group I; 72% for group II and 56% for group III. During the 6-24 hours period incidence of emesis-free patients were 96% for group I; 56% for group II and 32% for group III. So to conclude, a single dose of palanosetron (0.25 mg) is a superior anti-emetic to granisetron (3.0 mg) or ondansetron (8.0 mg) in complete prevention of postoperative nausea and vomiting after middle ear surgery during the first 24 hours period.

Boccia RV, Gordan LN, Clark G, Howell JD, Grunberg SM, Sancuso Study G. Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. *Support Care Cancer*. 2011;19(10):1609-1617.

PURPOSE: A novel transdermal formulation of granisetron (the granisetron transdermal delivery system (GTDS)) has been developed to deliver granisetron continuously over 7 days. This double-blind, phase III, non-inferiority study compared the efficacy and tolerability of the GTDS to daily oral granisetron for the control of chemotherapy-induced nausea and vomiting (CINV)., PATIENTS AND METHODS: Six hundred forty-one patients were randomized to oral (2 mg/day, 3-5 days) or transdermal granisetron (one GTDS patch, 7 days), before receiving multi-day chemotherapy. The primary endpoint was complete control of CINV (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final administration. The prespecified non-inferiority margin was 15%., RESULTS: Five hundred eighty-two patients were included in the per protocol analysis. The GTDS displayed non-inferiority to oral granisetron: complete control was achieved by 60% of patients in the GTDS group, and 65%

in the oral granisetron group (treatment difference, -5%; 95% confidence interval, -13-3). Both treatments were well tolerated, the most common adverse event being constipation., CONCLUSIONS: The GTDS provides effective, well-tolerated control of CINV associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron.

Candiotti KA, Ahmed SR, Cox D, Gan TJ. Palonosetron versus ondansetron as rescue medication for postoperative nausea and vomiting: a randomized, multicenter, open-label study. *BMC Pharmacol Toxicolo.* 2014;15:45.

BACKGROUND: This study compared palonosetron and ondansetron as rescue medications for postoperative nausea and vomiting (PONV) in patients who received prophylactic ondansetron. Although guidelines recommend use of an agent from a different class when prophylaxis has failed, palonosetron has unique properties relative to other serotonin 5-HT3 receptor antagonists. Prior trials assessing its use for rescue have had conflicting results. Although palonosetron has compared favorably with ondansetron for PONV prevention, the drugs have not been compared in the rescue setting of failure of 5-HT3 receptor antagonist prophylaxis., METHODS: This was a randomized, open-label, multicenter trial comparing the efficacy and safety of intravenous palonosetron 0.075 mg and intravenous ondansetron 4 mg in patients experiencing PONV following laparoscopic abdominal or gynecological surgery despite prophylactic ondansetron., RESULTS: Of 239 patients screened, 220 were enrolled and 98 were treated for PONV: 48 and 50 in the palonosetron and ondansetron arms, respectively. Complete control during 72 hours after study drug administration was achieved in 25.0% of palonosetron recipients and 18.0% of ondansetron recipients (95% confidence interval [CI], -9.2, 23.3; p=0.40). Corresponding incidences of vomiting were 29.2% for palonosetron and 48.0% for ondansetron (95% CI, -0.06, 37.7; p=0.057), and 62.5% and 56.0% required additional rescue treatment, respectively (95% CI, -25.9, 12.9; p=0.52). Other than a similar incidence of procedural pain in the 2 groups, the most common treatment-emergent adverse events, which were generally mild, were headache (14.6% vs 12.0%), constipation (8.3% vs 10.0%), and dizziness (6.3% vs 8.0%), for the palonosetron and ondansetron groups, respectively., CONCLUSIONS: Palonosetron and ondansetron did not show differences in the primary efficacy endpoint of CC during the 72 hours after study drug administration. There was a trend toward less emesis in the 0-72 h time period favoring palonosetron. While larger studies are needed to fully assess any clinical benefits of palonosetron to rescue patients who have failed ondansetron prophylaxis for PONV, the benefit, if any, would be limited based on this study., TRIAL REGISTRATION: ClinicalTrials.gov, NCT00967499 (Registered August 27, 2009).

Dabbous AS, Jabbour-Khoury SI, Nasr VG, et al. Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery. *Middle East J Anaesthesiol.* 2010;20(4):565-570.

In a prospective randomized double-blind study, we compared the effectiveness of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery. Hundred ASA I and II patients scheduled for laparoscopic surgery were enrolled in the study and 84 patients completed it. Following induction of anesthesia, group I (n=42) received granisetron 1 mg and dexamethasone 8 mg, group II (n=42) received ondansetron 4 mg and dexamethasone 8 mg. Nausea and vomiting episodes, pain scores as well as side effects were recorded during the first hour and subsequently during the first 6 and 24 hours postoperatively. Satisfaction scores were obtained at discharge. There was no statistically significant difference between the 2 groups during the 1st 24 hours following surgery in regards to pain scores, satisfaction and side effects manifestations. At 0-1 hour interval, 100% of patients in group I and 97.6% in group II had no vomiting. Total response (no moderate or severe nausea and no rescue antiemetics) was 83.3% in group I and 80.95% in group II, and metoclopramide was used in 7.1% of patients in both groups. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II. At 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. In conclusion, the combination of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg following induction of anesthesia in patients undergoing laparoscopic surgery showed no statistically significant difference in antiemetic efficacy with minimal side effects and excellent patient satisfaction.

Gan TJ, Gu J, Singla N, et al. Rolapitant for the prevention of postoperative nausea and vomiting: a prospective, double-blinded, placebo-controlled randomized trial. *Anesth Analg*. 2011;112(4):804-812.

BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after surgery. Neurokinin-1 (NK(1)) receptor antagonists have been shown to be safe and effective for the prevention and treatment of PONV in humans. Rolapitant is a potent, selective NK1 receptor antagonist that is rapidly absorbed, has a remarkably long half-life (up to180 hours), and appears to have a low potential for drug-drug interactions. We evaluated the dose response for rolapitant for the prevention of PONV in subjects at high risk for this condition, and rolapitant's effects on preventing delayed PONV were explored up to 5 days after surgery., METHODS: A randomized, multicenter, double-blind, dose-ranging study of rolapitant was conducted with placebo and active control groups. Six hundred nineteen adult women undergoing open abdominal surgery were randomly assigned in equal ratios to 1 of 6 study arms: oral rolapitant in 5-mg, 20-mg, 70-mg, or 200-mg doses; IV ondansetron 4 mg; or placebo, stratified by history of PONV or motion sickness. The primary study endpoint was absence of emetic episodes, regardless of use of rescue medication, at 24 hours after extubation., RESULTS: Groups assigned to rolapitant 20-mg, 70-mg, and 200-mg had a higher incidence of no emesis in comparison

with placebo at 24 hours after surgery. A linear relationship between rolapitant dose and primary outcome was seen. The probability of an emetic episode was significantly lower in the rolapitant 70-mg and 200-mg groups in comparison with placebo (P <= 0.001 based on the log-rank test). No significant differences were noted between rolapitant and the active control (ondansetron) at 24 hours after surgery, but there was a higher incidence of no emesis (regardless of rescue medication use) in the rolapitant 200- and 70-mg groups at 72 and 120 hours, respectively., CONCLUSION: Rolapitant is superior to placebo in reducing emetic episodes after surgery and reduces the incidence of vomiting in a dose-dependent manner. No differences in side effect profile were observed between rolapitant and placebo.

Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol.* 2014;25(7):1333-1339.

BACKGROUND: Safe, effective and convenient antiemetic regimens that preserve benefit over repeated cycles are needed for optimal supportive care during cancer treatment. NEPA, an oral fixed-dose combination of netupitant, a highly selective NK1 receptor antagonist (RA), and palonosetron (PALO), a distinct 5-HT3 RA, was shown to be superior to PALO in preventing chemotherapy-induced nausea and vomiting after a single cycle of highly (HEC) or moderately (MEC) emetogenic chemotherapy in recent trials. This study was designed primarily to assess the safety but also to evaluate the efficacy of NEPA over multiple cycles of HEC and MEC., PATIENTS AND METHODS: This multinational, double-blind, randomized phase III study (NCT01376297) in 413 chemotherapy-naive patients evaluated a single oral dose of NEPA (NETU 300 mg + PALO 0.50 mg) given on day 1 with oral dexamethasone (DEX). An oral 3-day aprepitant (APR) regimen + PALO + DEX was included as a control (3:1 NEPA:APR randomization). In HEC, DEX was administered on days 1-4 and in MEC on day 1. Safety was assessed primarily by adverse events (AEs), including cardiac AEs; efficacy by complete response (CR: no emesis, no rescue)., RESULTS: Patients completed 1961 total chemotherapy cycles (76% MEC, 24% HEC) with 75% completing >=4 cycles. The incidence/type of AEs was comparable for both groups. Most frequent NEPA-related AEs included constipation (3.6%) and headache (1.0%); there was no indication of increasing AEs over multiple cycles. The majority of AEs were mild/moderate and there were no cardiac safety concerns based on AEs and electrocardiograms. The overall (0-120 h) CR rates in cycle 1 were 81% and 76% for NEPA and APR + PALO, respectively, and antiemetic efficacy was maintained over repeated cycles., CONCLUSIONS: NEPA, a convenient single oral dose antiemetic targeting dual pathways, was safe, well tolerated and highly effective over multiple cycles of HEC/MEC.

Grover VK, Mathew PJ, Hegde H. Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study. *Anaesthesia.* 2009;64(6):595-600.

Peri-operative prophylactic anti-emetics are commonly used parenterally. Orally disintegrating ondansetron is efficacious during chemotherapy. Therefore, we aimed to study the efficacy of orally disintegrating ondansetron for postoperative nausea and vomiting. In a randomised, double-blind, placebo controlled trial on 109 patients scheduled for laparoscopic cholecystectomy, oral ondansetron was compared to intravenous ondansetron and placebo. The anaesthetic technique was standardised. Mean time (SD) to tolerating oral intake was delayed in the placebo group to 366.1 (77.6) min compared to oral 322.9 (63.7) min and intravenous 322.4 (65.2) min groups. This is corroborated by a higher incidence of nausea and vomiting in the control group during the first 6 h postoperatively (control 44.4%, oral 17.7%, intravenous 18.2%). There was no significant difference between oral and intravenous groups. In conclusion, orally disintegrating ondansetron was as efficacious as intravenous ondansetron in the peri-operative phase and may be a viable option for prophylaxis of emesis in day care surgery.

Habib AS, Keifer JC, Borel CO, White WD, Gan TJ. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. *Anesth Analg.* 2011;112(4):813-818.

BACKGROUND: Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 hours. In addition to causing patient discomfort, the physical act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery, aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 hours postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia., METHODS: Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 hours after surgery. Statistical analysis was performed using Wilcoxon's ranked sum test and chi(2) test. $P < 0.05$ was considered statistically significant., RESULTS: One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($P = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% vs. 21%, $P = 0.0419$) and 24 hours (14% vs. 36%, $P = 0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs. 60%),

nausea scores, need for rescue antiemetics (65% vs. 60%), complete response (no PONV and no rescue, 22% vs. 36%), or patient satisfaction with the management of PONV., CONCLUSION: The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

Jain V, Mitra JK, Rath GP, Prabhakar H, Bithal PK, Dash HH. A randomized, double-blinded comparison of ondansetron, granisetron, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. *J Neurosurg Anesth*. 2009;21(3):226-230.

Postoperative nausea and vomiting (PONV) are frequent and distressing complications after neurosurgical procedures. We evaluated the efficacy of ondansetron and granisetron to prevent PONV after supratentorial craniotomy. In a randomized double-blind, placebo controlled trial, 90 adult American Society of Anesthesiologists I, II patients were included in the study. A standard anesthesia technique was followed. Patients were divided into 3 groups to receive either placebo (saline), ondansetron 4 mg, or granisetron 1 mg intravenously at the time of dural closure. After extubation, episodes of nausea and vomiting were noted for 24 hours postoperatively. Statistical analysis was performed using chi2 test and 1-way analysis of variance. Demographic data, duration of surgery, intraoperative fluids and analgesic requirement, and postoperative pain (visual analog scale) scores were comparable in all 3 groups. It was observed that the incidence of vomiting in 24 hours, severe emetic episodes, and requirement of rescue antiemetics were less in ondansetron and granisetron groups as compared with placebo ($P<0.001$). Both the study drugs had comparable effect on vomiting. However, the incidence of nausea was comparable in all 3 groups ($P=0.46$). A favorable influence on the patient satisfaction scores, and number needed to prevent emesis was seen in the 2 drug groups. No significant correlation was found between neurosurgical factors (presence of midline shift, mass effect, pathologic diagnosis of tumor, site of tumor) and the occurrence of PONV. We conclude that ondansetron 4 mg and granisetron 1 mg are comparably effective at preventing emesis after supratentorial craniotomy. However, neither drugs prevented nausea effectively.

Kaushal J, Gupta MC, Kaushal V, et al. Clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer. *Singap Med J.* 2010;51(11):871-875.

INTRODUCTION: Palonosetron and ondansetron are two selective 5-hydroxytryptamine (5-HT3) receptor antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of moderately emetic anticancer chemotherapy. Their efficacy is enhanced by the concurrent administration of dexamethasone. In the present study, we aimed to compare the antiemetic efficacy of a palonosetron plus dexamethasone (PD) schedule versus

an ondansetron plus dexamethasone (OD) schedule., METHODS: A randomised, crossover trial was conducted in 30 patients with head and neck cancer who were receiving moderately emetogenic chemotherapy. The patients were divided into two groups. In the first cycle, one group was given a PD schedule and the other, an OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases., RESULTS: Complete response in the acute phase was observed in 83.3 percent of the patients on the PD schedule and in 80 percent of those on the OD schedule. In the delayed phase, complete response was observed in 76.7 percent and 66.7 percent of the patients on the PD schedule and OD schedule, respectively. The overall rate of complete response was 66.7 percent in the PD group and 46.7 percent in the OD group. In the PD group, there were 73.3 percent of nausea-free patients as opposed to 66.7 percent in the OD group., CONCLUSION: The results suggest that the PD schedule was superior to the OD schedule in controlling emesis in cancer chemotherapy, although this difference was not statistically significant.

Kim JE, Hong YS, Lee JL, et al. A randomized study of the efficacy and safety of transdermal granisetron in the control of nausea and vomiting induced by moderately emetogenic chemotherapy in Korean patients. *Support Care Cancer.* 2015;23(6):1769-1777.

BACKGROUND: The granisetron transdermal system (GTS) showed non-inferior efficacy to oral granisetron to control chemotherapy-induced nausea and vomiting (CINV) during multiday chemotherapy. We compared the efficacy and safety of GTS with that of intravenous and oral granisetron in Korean patients receiving moderately emetogenic chemotherapy (MEC). PATIENTS AND METHODS: A total of 276 patients were randomized into GTS (n = 139, one patch on days 1-4) or control group (n = 137, intravenous on day 1 and oral on days 2-4). The primary endpoint was the percentage of patients achieving complete response (CR) from chemotherapy initiation until 24 h after the final administration. RESULTS: Out of 234 patients (112 in GTS and 122 in control group) included in the per protocol analysis, 97.9 % had gastrointestinal cancer and 76.9 % received 3-day chemotherapy. The GTS showed non-inferior efficacy achieving CR in 75.0 % of the patients; 74.6 % of the patients in the control group achieved CR (95 % confidence interval -10.73 to 11.55 %). The CR rate did not change after subgroup analyses by sex, age, and chemotherapy naivety and analysis per day and overall days of treatment. The GTS group showed sustained CR from day 1 to day 4. Patients' satisfaction, assessed using Functional Living Index-Emesis (FLI-E), showed no difference. Both treatments were well tolerated and safe. CONCLUSION: The GTS showed non-inferior efficacy to intravenous and oral granisetron. The safety, tolerability, and FLI-E scores of the GTS were comparable to those of control group. The GTS offers a convenient alternative option for relieving CINV in patients receiving MEC.

Kim JS, Baek JY, Park SR, et al. Open-label, randomized comparison of the efficacy of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed cisplatin-induced emesis in cancer patients. *Cancer Res Treat.* 2004;36(6):372-376.

PURPOSE: The aim of this study is to compare the antiemetic efficacy and tolerability of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed emesis. MATERIAL AND METHODS: From April 2002 through October 2002, a total of 112 patients receiving cisplatin- based combination chemotherapy were randomized to receive a single i.v. dose of dolasetron 100 mg or ondansetron 8 mg, 30 minutes before the initiation of chemotherapy. In the ondansetron group, two additional doses of ondansetron 8 mg were given at intervals of 2 to 4 hours. To prevent delayed emesis, dolasetron 200 mg p.o. daily or ondansetron 8 mg p.o. bid was administered from the 2(nd) days to a maximum of 5 days. The primary end point was the proportion of patients that experienced no emetic episodes and required no rescue medication (complete response, CR) during the 24 hours (acute period) and during Day 2 to Day 5+/-2 days (delayed period), after chemotherapy. The secondary end points included the incidence and severity of emesis. RESULTS: 105 patients were evaluable for efficacy. CR rates during the acute period were 36.0% for a single dose of dolasetron 100 mg, and 43.6% for three doses of ondansetron 8 mg. CR rates during the delayed period were 8.0% and 10.9%, respectively. There was no significant difference in the efficacy between the two groups. Adverse effects were mostly mild to moderate and not related to study medication. CONCLUSIONS: A single i.v. dose of dolasetron 100 mg is as effective as three i.v. doses of ondansetron 8 mg in preventing acute and delayed emesis after cisplatin-based chemotherapy, with a comparable safety profile.

Kim SH, Hong JY, Kim WO, Kil HK, Karm MH, Hwang JH. Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a prospective, randomized, double-blinded study. *Korean J Anesthesiol.* 2013;64(6):517-523.

BACKGROUND: Postoperative nausea and vomiting (PONV) continues to be a major problem, because PONV is associated with delayed recovery and prolonged hospital stay. Although the PONV guidelines recommended the use of 5-hydroxy-tryptamine (5-HT3) receptor antagonists as the first-line prophylactic agents in patients categorized as high-risk, there are few studies comparing the efficacies of ondansetron, ramosetron, and palonosetron. The aim of present study was to compare the prophylactic antiemetic efficacies of three 5HT3 receptor antagonists in high-risk patients after laparoscopic surgery. METHODS: In this prospective, randomized, double-blinded trial, 109 female nonsmokers scheduled for elective laparoscopic surgery were randomized to receive intravenous 4 mg ondansetron (n = 35), 0.3 mg ramosetron (n = 38), or 75 microg palonosetron (n = 36) before anesthesia. Fentanyl-based intravenous patient-controlled analgesia was administered for 48 h after surgery. Primary antiemetic efficacy variables were the incidence and severity of nausea, the frequency of emetic episodes during the first 48 h after surgery, and the need to use a rescue antiemetic medication. RESULTS: The

overall incidence of nausea/retching/vomiting was lower in the palonosetron (22.2%/11.1%/5.6%) than in the ondansetron (77.1%/48.6%/28.6%) and ramosetron (60.5%/28.9%/18.4%) groups. The rescue antiemetic therapy was required less frequently in the palonosetron group than the other groups (P < 0.001). Kaplan-Meier analysis showed that the order of prophylactic efficacy in delaying the interval to use of a rescue emetic was palonosetron, ramosetron, and ondansetron. CONCLUSIONS: Single-dose palonosetron is the prophylactic antiemetics of choice in high-risk patients undergoing laparoscopic surgery.

Kim YY, Moon SY, Song DU, Lee KH, Song JW, Kwon YE. Comparison of palonosetron with ondansetron in prevention of postoperative nausea and vomiting in patients receiving intravenous patient-controlled analgesia after gynecological laparoscopic surgery. *Korean J Anesthesiol.* 2013;64(2):122-126.

BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after anesthesia and surgery. This study was designed to compare the effects of palonosetron and ondansetron in preventing PONV in high-risk patients receiving intravenous opioid-based patient-controlled analgesia (IV-PCA) after gynecological laparoscopic surgery. METHODS: One hundred non-smoking female patients scheduled for gynecological laparoscopic surgery were randomly assigned into the palonosetron group (n = 50) or the ondansetron group (n = 50). Palonosetron 0.075 mg was injected as a bolus in the palonosetron group. Ondansetron 8 mg was injected as a bolus and 16 mg was added to the IV-PCA in the ondansetron group. The incidences of nausea, vomiting and side effects was recorded at 2 h, 24 h, 48 h and 72 h, postoperatively. RESULTS: There were no significant differences between the groups in the incidence of PONV during 72 h after operation. However, the incidence of vomiting was lower in the palonosetron group than in the ondansetron group (18% vs. 4%, P = 0.025). No differences were observed in use of antiemetics and the side effects between the groups. CONCLUSIONS: The effects of palonosetron and ondansetron in preventing PONV were similar in high-risk patients undergoing gynecological laparoscopic surgery and receiving opioid-based IV-PCA.

Kimura H, Yamamoto N, Shirai T, et al. Efficacy of triplet regimen antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) in bone and soft tissue sarcoma patients receiving highly emetogenic chemotherapy, and an efficacy comparison of single-shot palonosetron and consecutive-day granisetron for CINV in a randomized, single-blinded crossover study. *Cancer Med-US.* 2015;4(3):333-341.

The first aim of this study was to evaluate combination antiemetic therapy consisting of 5-HT3 receptor antagonists, neurokinin-1 receptor antagonists (NK-1RAs), and dexamethasone for multiple high emetogenic risk (HER) anticancer agents in bone and soft tissue sarcoma. The second aim was to compare the effectiveness of single-shot palonosetron and consecutive-day granisetron in a randomized, single-blinded crossover study. A single randomization method was used to assign eligible patients to the palonosetron or granisetron arm. Patients in the palonosetron arm received a palonosetron regimen during the first and third chemotherapy

courses and a granisetron regimen during the second and fourth courses. All patients received NK-1RA and dexamethasone. Patients receiving the palonosetron regimen were administered 0.75 mg palonosetron on day 1, and patients receiving the granisetron regimen were administered 3 mg granisetron twice daily on days 1 through 5. All 24 patients in this study received at least 4 chemotherapy courses. A total of 96 courses of antiemetic therapy were evaluated. Overall, the complete response CR rate (no emetic episodes and no rescue medication use) was 34%, while the total control rate (a CR plus no nausea) was 7%. No significant differences were observed between single-shot palonosetron and consecutive-day granisetron. Antiemetic therapy with a 3-drug combination was not sufficient to control chemotherapy-induced nausea and vomiting (CINV) during chemotherapy with multiple HER agents for bone and soft tissue sarcoma. This study also demonstrated that consecutive-day granisetron was not inferior to single-shot palonosetron for treating CINV.

Laha B, Hazra A, Mallick S. Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: a randomized controlled trial. *Indian J Pharmacol.* 2013;45(1):24-29.

OBJECTIVES: Incidence of postoperative nausea and vomiting (PONV), without active intervention, following laparoscopic cholecystectomy is unacceptably high. We evaluated the effectiveness of intravenous (IV) palonosetron in counteracting PONV during the first 24 hrs following laparoscopic cholecystectomy, using ondansetron as the comparator drug., MATERIALS AND METHODS: In a randomized, controlled, single blind, parallel group trial, single pre-induction IV doses of palonosetron (75 mcg) or ondansetron (4 mg) were administered to adult patients of either sex undergoing elective laparoscopic cholecystectomy. There were 49 subjects per group. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary effectiveness measure was total number of PONV episodes in the 24 hrs period following end of surgery. The frequencies of individual nausea, retching and vomiting episodes, visual analog scale (VAS) score for nausea at 2, 6 and 24 hrs, use of rescue antiemetic (metoclopramide), number of complete responders (no PONV or use of rescue in 24 hrs) and adverse events were secondary measures., RESULTS: There was no statistically significant difference between the groups in primary outcome. Similarly, the frequencies of nausea, retching and vomiting episodes, when considered individually, did not show significant difference. Nausea score was comparable at all time points. With palonosetron, 14 subjects (28.6%) required rescue medication while 13 (26.5%) did so with ondansetron. The number of complete responders was 14 (28.6%) and 16 (32.7%), respectively. Adverse events were few and mild. QTc prolongation was not encountered., CONCLUSION: Palonosetron is comparable to ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.

Mandanas RA, Beveridge R, Rifkin RM, Wallace H, Greenspan A, Asmar L. A randomized, multicenter, open-label comparison of the antiemetic efficacy of dolasetron versus

ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy. *Support Cancer Ther.* 2005;2(2):114-121.

This study assessed the efficacy and safety of dolasetron compared with ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy followed by peripheral blood stem cell support. Twenty centers randomized 197 patients to receive dolasetron 100 mg intravenously (I.V.) followed 8-12 hours later by a single oral dose of dolasetron 100 mg or ondansetron 32 mg I.V., followed 8-12 hours later by a single oral dose of ondansetron 8 mg during high-dose chemotherapy (HDC) regimens for breast cancer (n = 96; 48.7%), non-Hodgkin's lymphoma (n = 83; 42.1%), or Hodgkin's disease (n = 18; 9.1%). All patients received a daily I.V. bolus of dexamethasone 10 mg with study antiemetic agents and a continuous infusion of diphenhydramine, lorazepam, and dexamethasone (ie, BAD pump) throughout the course of the study, with patient-controlled on-demand bolus doses as needed. After completing a daily diary of emetic episodes and rescue medication use, 164 of 197 patients were evaluable. Total plus complete responses (no emesis, no nausea, no rescue) over the entire study period were achieved in 45.7% and 46.9% of patients on the dolasetron and ondansetron arms, respectively. Dolasetron and ondansetron were well-tolerated. This study demonstrates that dolasetron and ondansetron are equally safe and effective in the prevention of nausea and vomiting associated with HDC (P = 0.955).

Mattiuzzi GN, Cortes JE, Blamble DA, et al. Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. *Cancer.* 2010;116(24):5659-5666.

BACKGROUND: Nausea and vomiting in patients with acute myelogenous leukemia (AML) can be from various causes, including the use of high-dose cytarabine., METHODS: The authors compared 2 schedules of palonosetron versus ondansetron in the treatment of chemotherapy-induced nausea and vomiting (CINV) in patients with AML receiving high-dose cytarabine. Patients were randomized to: 1) ondansetron, 8 mg intravenously (IV), followed by 24 mg continuous infusion 30 minutes before high-dose cytarabine and until 12 hours after the high-dose cytarabine infusion ended; 2) palonosetron, 0.25 mg IV 30 minutes before chemotherapy, daily from Day 1 of high-dose cytarabine up to Day 5; or 3) palonosetron, 0.25 mg IV 30 minutes before high-dose cytarabine on Days 1, 3, and 5., RESULTS: Forty-seven patients on ondansetron and 48 patients on each of the palonosetron arms were evaluable for efficacy. Patients in the palonosetron arms achieved higher complete response rates (no emetic episodes plus no rescue medication), but the difference was not statistically significant (ondansetron, 21%; palonosetron on Days 1-5, 31%; palonosetron on Days 1, 3, and 5, 35%; P = .32). Greater than 77% of patients in each arm were free of nausea on Day 1; however, on Days 2 through 5, the proportion of patients without nausea declined similarly in all 3 groups. On Days 6 and 7, significantly more patients receiving palonosetron on Days 1 to 5 were free of nausea (P = .001 and P = .0247, respectively)., CONCLUSIONS: The daily assessments of emesis did not show significant differences between the study arms. Patients receiving palonosetron on Days 1 to 5 had

significantly less severe nausea and experienced significantly less impact of CINV on daily activities on Days 6 and 7.Copyright Cancer 2010. © 2010 American Cancer Society.

Metaxari M, Papaioannou A, Petrou A, Chatzimichali A, Pharmakalidou E, Askitopoulou H. Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents. *J Anesth.* 2011;25(3):356-362.

PURPOSE: The aim of this double-blind randomized study was to compare the antiemetic efficacy of three 5-hydroxytryptamine type 3 antagonists in terms of the incidence and intensity of postoperative nausea and vomiting (PONV) in a homogenous group of female patients undergoing thyroidectomy., METHODS: The study cohort consisted of 203 American Society of Anesthesiologists PS I-II female patients randomized into four groups to receive at induction of anesthesia an intravenous (IV) bolus of 5 ml solution of one of the following: normal saline (placebo), granisetron 3 mg, ondansetron 4 mg, or tropisetron 5 mg. Nausea and vomiting were evaluated at five time points: during the first hour in the postanesthesia care unit (PACU) and 6, 12, 18, and 24 h postoperatively. Nausea intensity was measured using a visual analogue scale score (0-10)., RESULTS: Patients in the placebo group displayed a high incidence of nausea in the PACU and at 6, 12, and 18 h postoperatively (44, 60, 50, and 34%, respectively) and of vomiting (26, 42, 30 and 10%). The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 h (26, 18, and 2%, respectively) and vomiting at 6 and 12 h (10 and 6%, respectively). Ondansetron reduced significantly the incidence of nausea and vomiting only at 6 h postoperatively (28 and 12%, respectively). The administration of tropisetron did not affect the incidence of PONV compared to placebo., CONCLUSION: Among the female patients of this study undergoing thyroid surgery, granisetron 3 mg provided the best prophylaxis from PONV. Ondansetron 4 mg was equally effective, but its action lasted only 6 h, whereas tropisetron 5 mg was found ineffective.

Moon HY, Baek CW, Choi GJ, et al. Palonosetron and aprepitant for the prevention of postoperative nausea and vomiting in patients indicated for laparoscopic gynaecologic surgery: a double-blind randomised trial. *BMC Anesthesiol.* 2014;14:68.

BACKGROUND: Postoperative nausea and vomiting (PONV) is one of the most common postsurgical complications. Palonosetron, a 5-hydroxytryptamine receptor antagonist, is effective for PONV prevention. Herein, we compared palonosetron and aprepitant (a neurokinin-1 receptor antagonist) for PONV prevention in patients indicated for laparoscopic gynaecologic surgery., METHODS: Ninety-three patients who were scheduled to undergo laparoscopic gynaecologic surgery under general anaesthesia were assigned to receive either a single intravenous injection of 0.075-mg palonosetron or 40-mg oral aprepitant in a double-blind randomised trial. The primary efficacy end points included complete response (visual analogue scale [VAS] nausea score <4 and no use of rescue therapy) 0-48 h after surgery. Nausea severity (0-10) and use of rescue therapy were monitored for 0-48 h. The secondary efficacy end points were the effect of aprepitant quantified using a 10-point VAS for pain, consumption of

intravenous patient-controlled analgesia, and use of rescue analgesics., RESULTS: Aprepitant was non-inferior to palonosetron in terms of complete response 0-48 hours after surgery (74% vs. 77%). At 0 and 2 h after administration, the nausea severity with 40-mg aprepitant was significantly lesser than that with 0.075-mg palonosetron (P<0.05). At 6 and 24 h after administration, fentanyl consumption with 40-mg aprepitant was significantly lower than that with 0.075-mg palonosetron. Greater amounts of rescue analgesics were required in the aprepitant group., CONCLUSIONS: Palonosetron and aprepitant were both effective for PONV prevention in the patients indicated for laparoscopic gynaecologic surgery. The drugs can be used in combination for multimodal therapy because they bind to different receptors. More research is needed to evaluate the effects of aprepitant on pain management in humans.

Moon YE, Joo J, Kim JE, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. *Brit J Anaesth.* 2012;108(3):417-422.

BACKGROUND: Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking. This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy., METHODS: A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue anti-emetics, and adverse effects were evaluated during 0-2 and 2-24 h., RESULTS: The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, P=0.045). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2-24 h. The only difference in the use of rescue anti-emetics was at 2-24 h (10% with palonosetron compared with 28% with ondansetron, P=0.02)., CONCLUSIONS: Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2-24 h after surgery.

Nakagaki M, Barras M, Curley C, Butler JP, Kennedy GA. A randomized trial of olanzapine versus palonosetron versus infused ondansetron for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients undergoing hematopoietic stem cell transplantation. *Support Care Cancer.* 2017;25(2):607-613.

PURPOSE: The primary aim of this study was to compare the effectiveness of olanzapine, palonosetron and ondansetron infusion (standard of care) for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) in patients undergoing hematopoietic stem

cell transplantation (HSCT)., METHOD: It was a randomized open-label prospective study. Sixty-two patients were randomized to receive either ondansetron 32-mg infusion over 24 h, or olanzapine wafer 10 mg once daily in addition to ondansetron 8 mg IV three times a day or a single dose of palonosetron 0.25 mg IV instead of ondansetron. All groups were allowed rescue antiemetics. The primary endpoint was a composite outcome of no emesis, no use of rescue medication, and nausea score reduction of >=50 %. The secondary endpoint was nausea score reduction of >=50 %. Both endpoints were measured at 24 and 48 h after initiation of the study treatment. Statistical analysis was conducted using a double-sided Fisher's exact test., RESULT: The primary endpoint was achieved in 6, 45, and 18 %, and 6, 64, and 18 % of ondansetron versus olanzapine versus palonosetron patient groups at 24 and 48 h, respectively. The secondary outcome was observed in 17, 60, and 62 %, and 35, 71, and 43 % of ondansetron versus olanzapine versus palonosetron patient groups at 24 and 48 h, respectively. Serious adverse drug reactions were not reported in any arms. Time to engraftment was not significantly different between the arms., CONCLUSIONS: Olanzapine was an effective treatment of breakthrough CINV. A single dose of palonosetron significantly reduced nausea up to 24 h.

Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. *Obstet Gynecol.* 2014;124(4):735-742.

OBJECTIVE: To evaluate whether ondansetron or the combination of doxylamine and pyridoxine was superior for the treatment of nausea and vomiting of pregnancy., METHODS: This was a double-blind, randomized, controlled trial in which women with nausea and vomiting of pregnancy were assigned to 4 mg of ondansetron plus a placebo tablet or 25 mg pyridoxine plus 12.5 mg of doxylamine for 5 days. The primary outcome was an improvement in nausea as reported on a 100-mm visual analog scale (VAS). Secondary outcomes were a reduction in vomiting on the VAS and the proportion of patients reporting sedation or constipation while using either study regimen., RESULTS: Thirty-six women (18 in each group) were randomized to either ondansetron or pyridoxine and doxylamine, of whom 13 (72%) and 17 (94%) completed follow-up, respectively. There were no differences among the groups with regard to demographic characteristics or baseline nausea. Patients randomized to ondansetron were more likely to have an improvement in their baseline nausea as compared with those using pyridoxine and doxylamine over the course of 5 days of treatment (median VAS score decreased 51 mm [interquartile range 37-64] compared with 20 mm [8-51]; P=.019). Furthermore, women using ondansetron reported less vomiting (median VAS decreased 41 [interquartile range 17-57] compared with 17 [-4 to 38]; P=.049). There was no significant difference between the groups regarding sedation or constipation., CONCLUSION: Our investigation showed ondansetron to be superior to the combination of pyridoxine and doxylamine in the treatment of nausea and emesis in pregnancy., CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01668069., LEVEL OF EVIDENCE: : I.

Park SK, Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery. *J Int Med Res.* 2011;39(2):399-407.

This randomized, double-blind study evaluated the relative efficacy of palonosetron (a new, selective 5-hydroxytryptamine type 3 [5-HT(3)] receptor antagonist) and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 45) or ondansetron 8 mg (n = 45), intravenously, immediately before induction of general anaesthesia. The occurrence of nausea and vomiting and the severity of nausea according to a visual analogue scale were monitored immediately after the end of surgery and during the following 24 h. The incidence of PONV was significantly lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale for nausea. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.

Raftopoulos H, Cooper W, O'Boyle E, Gabrail N, Boccia R, Gralla RJ. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. *Support Care Cancer.* 2015;23(3):723-732.

PURPOSE: Subcutaneous APF530 provides controlled sustained release of granisetron to prevent acute (0-24 h) and delayed (24-120 h) chemotherapy-induced nausea and vomiting (CINV). This randomized, double-blind phase 3 trial compared APF530 and palonosetron in preventing acute and delayed CINV after moderately (MEC) or highly emetogenic chemotherapy (HEC)., METHODS: Patients receiving single-day MEC or HEC received single-dose APF530 250 or 500 mg subcutaneously (SC) (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg. Primary objectives were to establish APF530 noninferiority to palonosetron for preventing acute CINV following MEC or HEC and delayed CINV following MEC and to determine APF530 superiority to palonosetron for preventing delayed CINV following HEC. The primary efficacy end point was complete response (CR [using CI difference for APF530-palonosetron]). A lower confidence bound greater than -15 % indicated noninferiority., RESULTS: In the modified intent-to-treat population (MEC = 634; HEC = 707), both APF530 doses were noninferior to palonosetron in preventing acute CINV after MEC (CRs 74.8 % [-9.8, 9.3] and 76.9 % [-7.5, 11.4], respectively, vs. 75.0 % palonosetron) and after HEC (CRs 77.7 % [-11.5, 5.5] and 81.3 % [-7.7, 8.7], respectively, vs. 80.7 % palonosetron). APF530 500 mg was noninferior to palonosetron in preventing delayed CINV after MEC (CR 58.5 % [-9.5, 12.1] vs. 57.2 % palonosetron) but not superior in preventing delayed CINV after HEC. Adverse events were generally mild and unrelated to treatment, the most common (excluding injection-site reactions) being constipation., CONCLUSIONS: A single subcutaneous APF530 injection offers a convenient alternative to palonosetron for preventing acute and delayed CINV after MEC or HEC.

Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. *Lancet Oncol.* 2009;10(2):115-124.

BACKGROUND: Palonosetron is a second-generation 5-hydroxytryptamine 3 (5-HT(3))-receptor antagonist that has shown better efficacy than ondansetron and dolasetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy, and similar efficacy to ondansetron in preventing CINV in patients receiving highly emetogenic chemotherapy. In this phase III, multicentre, randomised, double-blind, double-dummy, stratified, parallel-group, active-comparator trial, we assessed the efficacy and safety of palonosetron versus granisetron for chemotherapy-induced nausea and vomiting, both of which were administered with dexamethasone in patients receiving highly emetogenic chemotherapy., METHODS: Between July 5, 2006, and May 31, 2007, 1143 patients with cancer who were receiving highly emetogenic chemotherapy (ie, cisplatin, or an anthracycline and cyclophosphamide combination [AC/EC]) were recruited from 75 institutions in Japan, and randomly assigned to either single-dose palonosetron (0.75 mg), or granisetron (40 microg/kg) 30 min before chemotherapy on day 1, both with dexamethasone (16 mg intravenously) on day 1 followed by additional doses (8 mg intravenously for patients receiving cisplatin or 4 mg orally for patients receiving AC/EC) on days 2 and 3. A non-deterministic minimisation method with a stochastic-biased coin was applied to the randomisation of patients. Covariates known to effect emetic risk, such as sex, age, and type of highly emetogenic chemotherapy, were used as stratification factors of minimisation to ensure balance between the treatment groups. Primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute phase (0-24 h postchemotherapy; non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24-120 h postchemotherapy; superiority comparison with granisetron). The non-inferiority margin was predefined in the study protocol as a 10% difference between groups in the proportion of patients with complete response. The palonosetron dose of 0.75 mg was chosen on the basis of two dose-determining trials in Japanese patients. All patients who received study treatment and highly emetogenic chemotherapy were included in the efficacy analyses (modified intention to treat). This trial is registered with ClinicalTrials.gov, number NCT00359567., FINDINGS: 1114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. 418 of 555 patients (75.3%) in the palonosetron group had complete response during the acute phase compared with 410 of 559 patients (73.3%) in the granisetron group (mean difference 2.9% [95% CI -2.70 to 7.27]). During the delayed phase, 315 of 555 patients (56.8%) had complete response in the palonosetron group compared with 249 of 559 patients (44.5%) in the granisetron group ($p<0.0001$). The main treatment-related adverse events were constipation (97 of 557 patients [17.4%] in the palonosetron group vs 88 of 562 [15.7%] in the granisetron group) and raised concentrations of serum aminotransferases

(aspartate aminotransferase: 24 of 557 [4.3%] vs 34 of 562 [6.0%]; alanine aminotransferase: 16 of 557 [2.9%] vs 33 of 562 [5.9%]); no grade 4 main treatment-related adverse events were reported., INTERPRETATION: When administered with dexamethasone before highly emetogenic chemotherapy, palonosetron exerts efficacy against chemotherapy-induced nausea and vomiting which is non-inferior to that of granisetron in the acute phase and better than that of granisetron in the delayed phase, with a comparable safety profile for the two treatments., FUNDING: Taiho Pharmaceutical (Tokyo, Japan).

Seol YM, Kim HJ, Choi YJ, et al. Transdermal granisetron versus palonosetron for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: a multicenter, randomized, open-label, cross-over, active-controlled, and phase IV study. *Support Care Cancer.* 2016;24(2):945-952.

BACKGROUND: Palonosetron is the second-generation 5-hydroxytryptamine 3 receptor antagonist (5-HT3RA) that has shown better efficacy than the first-generation 5-HT3RA for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy (MEC). Granisetron transdermal delivery system (GTDS), a novel transdermal formulation, was developed to deliver granisetron continuously over 7 days. This study compared the efficacy and tolerability of the GTDS to palonosetron for the control of CINV following MEC., MATERIAL AND METHOD: A total of 196 patients were randomized to GP or PG group. In this multicenter, randomized, open-label, cross-over, active-controlled, Phase IV study, GP group was assigned to receive transdermal granisetron (one GTDS patch, 7 days) in the first chemotherapy cycle, palonosetron (iv 0.25 mg/day, 1 days) in the second chemotherapy cycle before receiving MEC, and PG group was assigned to receive palonosetron in the first cycle and GTDS in the second cycle. Primary endpoint was the percentage of chemotherapy cycles achieving complete response (CR; defined as no emetic episodes and no rescue medication use) during the acute phase (0-24 h in post-chemotherapy; non-inferiority comparison with palonosetron)., RESULTS: Total 333 cycles (165 in GTDS and 168 in palonosetron) were included in the per protocol analysis. The GTDS cycles showed non-inferiority to palonosetron cycles during the acute phase: CR was achieved by 124 (75.2 %) patients in the GTDS cycles and 134 (79.8 %) patients in the palonosetron cycles (treatment difference, -4.6 %; 95 % confidence interval, -13.6-4.4). There was no significant difference in CR rate during acute phase after the end of the first and second chemotherapy cycle between GP and PG group ($p = 0.405$, $p = 0.074$). Patients' satisfaction, assessed using Functional Living Index-Emesis (FLI-E), GTDS cycle were higher than those of palonosetron cycle in GP group (FLI-E score; median 1549.5 in GTDS cycle, median 1670.0 in palonosetron cycle). Both treatments were well tolerated and safe., CONCLUSION: Transdermal granisetron is a good alternative therapeutic option to palonosetron for preventing CINV after MEC.

Siddique R, Hafiz MG, Rokeya B, Jamal CY, Islam A. Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia. *Mymensingh Med J.* 2011;20(4):680-688.

Effect of ondansetron and granisetron were evaluated in sixty (60) children (age 4-11 years) irrespective of sex, diagnosed case of acute lymphoblastic leukemia (ALL) who received high dose methotrexate and did not receive any antiemetic 24 hours prior to HDMTX. This was a prospective, randomized, double-blind, single center study. Of 60 children, 30 received oral ondansetron (4mg) and rest 30 granisetron (1mg) half an hour before therapy. Drugs were randomly allocated with appropriate code. The patients were followed up from day 1 to day 5 of therapy. Episodes of nausea and vomiting were recorded and scorings was done every 24 hours following chemotherapy. No significant difference was found between two groups according to acute emesis (Day-1) ($p=0.053$). In day two and day three it was significant ($p<0.05$). In day four it was significant ($p=0.002$). Early chemotherapy induced nausea and vomiting (CINV) were controlled 90% in children who received granisetron and 70% in children who received ondansetron. Delayed (Day 2-4) CINV were controlled in 80% of children who received granisetron and 43.4% who received ondansetron ($p<0.05$). Granisetron group required additional doses only 3.3% cases and ondanseton group 30% cases on the second day ($p<0.05$). Result was significant between two groups. About 36.7% patients had episodes of nausea on day four of chemotherapy in ondansetron group and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself ($p=0.001$). Maximum episodes of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% ($p=0.003$). Though adverse effects like headache, constipation, abdominal pain and loose motion were common in both group of children but their number was much less in children who received granisetron. On second day of therapy score of nausea and vomiting was maximum in ondansetron and minimum in granisetron treated on day 4 and the result was significant. So, to prevent acute and delayed CINV in children with ALL, oral graniseteron can be considered as more effective and well tolerated with minimum adverse effects compared with ondansetrons.

Soga T, Kume K, Kakuta N, et al. Fosaprepitant versus ondansetron for the prevention of postoperative nausea and vomiting in patients who undergo gynecologic abdominal surgery with patient-controlled epidural analgesia: a prospective, randomized, double-blind study. *J Anesth.* 2015;29(5):696-701.

PURPOSE: Postoperative nausea and vomiting (PONV) is the most common postoperative complication. The postoperative use of opioids is known to increase the incidence. We compared fosaprepitant, a neurokinin-1 (NK1) receptor antagonist, and ondansetron for their preventive effects on PONV in patients who underwent gynecologic abdominal surgery with patient-controlled epidural analgesia., METHODS: This prospective, double-blind, randomized study comprised 44 patients who underwent gynecologic abdominal surgery. They were randomly allocated to receive 150 mg intravenous fosaprepitant (n = 24; NKI group) or 4 mg ondansetron (n = 20; ONS group) before anesthesia, which was maintained with volatile anesthetics, remifentanil, fentanyl, and rocuronium. All patients received postoperative fentanyl by patient-controlled epidural anesthesia. The incidence of nausea and vomiting, complete response rate (i.e., no vomiting and no rescue antiemetic use), rescue antiemetic use, nausea

score (0-3), and visual analog scale score (VAS 0-10) for pain were recorded at 2, 24, 48, and 72 h after surgery., RESULTS: No (0 %) patient in the NKI group experienced vomiting after surgery; however, 4-6 (20-30 %) of 20 patients in the ONS group experienced vomiting. This difference was significant at 0-24, 0-48, and 0-72 h. During the study period, no significant differences existed between the NK1 and ONS groups in the incidence of PONV, complete response rate, rescue antiemetic use, nausea score, and VAS score for pain., CONCLUSION: Compared to ondansetron, fosaprepitant more effectively decreased the incidence of vomiting in patients who underwent gynecologic abdominal surgery with patient-controlled epidural analgesia.

Tan T, Ojo R, Immani S, Choroszczak P, Carey M. Reduction of severity of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine: a randomised comparison of prophylactic granisetron and ondansetron. *Int J Obstet Anesth.* 2010;19(1):56-60.

BACKGROUND: The incidence of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine may be 60-100%, and is a common cause of maternal dissatisfaction. Ondansetron has been shown to reduce pruritus but the effect is short-lived. The objective of this randomized double-blind trial was to evaluate the anti-pruritic efficacy of granisetron compared with ondansetron., METHODS: Eighty ASA I or II women undergoing elective caesarean section received spinal anaesthesia with 0.5% hyperbaric bupivacaine 10 mg, fentanyl 25 microg and preservative-free morphine 150 microg. After delivery of the baby and clamping of the umbilical cord, they were randomised to receive granisetron 3mg i.v. (group G) or ondansetron 8 mg i.v. (group O)., RESULTS: The two groups were similar for age, gestational age, height and weight. According to visual analogue pruritus scores, patients in group G experienced less pruritus at 8h (P=0.003) and 24h (P=0.01). Fewer patients in group G (n=8) than group O (n=18) required rescue anti-pruritic medication (P=0.03). Satisfaction scores were also higher in group G than in group O (P=0.03). There was no difference in overall incidence of pruritus, nausea and vomiting, and visual analogue pain scores between the two groups., CONCLUSIONS: Administration of granisetron 3mg i.v. reduces the severity of pruritus and the use of rescue anti-pruritic medication, and improves satisfaction but does not reduce the overall incidence of pruritus in women who have received subarachnoid morphine 150 microg compared to ondansetron 8 mg i.v.

Tian W, Wang Z, Zhou J, et al. Randomized, double-blind, crossover study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population. *Medical Oncol.* 2011;28(1):71-78.

The objective of this study was to compare the efficacy and tolerability of palonosetron and granisetron in a Chinese population receiving highly emetogenic cisplatin-based chemotherapy or moderately emetogenic chemotherapy. Patients were stratified by chemotherapy with cisplatin (yes/no) and then randomly assigned to receive either palonosetron (0.25 mg i.v.) in the first cycle followed by granisetron (3 mg i.v.) in the second cycle or vice versa. The primary

efficacy endpoint was the proportion of patients with complete response 0-24 h post-chemotherapy administration. The proportions of patients with complete response 24-120 and 0-120 h following chemotherapy were also compared. Of the 144 patients randomized, 36 (25%) received 60-80 mg/m(2) cisplatin; 66 of 72 patients in the palonosetron to granisetron group and 56 of 72 patients in the granisetron to palonosetron group completed treatment with both antiemetics. The efficacy and safety analyses included 128 palonosetron treatments and 138 granisetron treatments. Palonosetron consistently produced numerically higher complete response rates than granisetron in the acute phase (0-24 h, 71.09 vs. 65.22%), the delayed phase (24-120 h, 60.16 vs. 55.80%), and overall (0-120 h, 53.13 vs. 50.00%) though the differences were not significant. Both palonosetron and granisetron were well tolerated. Palonosetron was well tolerated and effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in a Chinese population. When used as monotherapy, 0.25-mg palonosetron was not inferior to 3-mg granisetron for preventing vomiting following highly or moderately emetogenic chemotherapy.

Tsutsumi YM, Kakuta N, Soga T, et al. The effects of intravenous fosaprepitant and ondansetron for the prevention of postoperative nausea and vomiting in neurosurgery patients: a prospective, randomized, double-blinded study. *BioMed Res Int.* 2014;2014:307025.

The incidence of postoperative nausea and vomiting (PONV) is 30-50% after surgery. PONV occurs frequently, especially after craniotomy. In this study, we investigated the preventive effects on PONV in a randomized study by comparing patients who had been administered fosaprepitant, a neurokinin-1 (NK1) receptor antagonist, or ondansetron intravenously. Sixty-four patients undergoing craniotomy were randomly allocated to receive fosaprepitant 150 mg i.v. (NK1 group, n = 32) or ondansetron 4 mg i.v. (ONS group, n = 32) before anesthesia. The incidence of vomiting was significantly less in the NK1 group, where 2 of 32 (6%) patients experienced vomiting compared to 16 of 32 (50%) patients in the ONS group during the first 24 and 48 hours following surgery. Additionally, the incidence of complete response (no vomiting and no rescue antiemetic use) was significantly higher in the NK1 group than in the ONS group, and was 66% versus 41%, respectively, during the first 24 hours, and 63% versus 38%, respectively, during the first 48 hours. In patients undergoing craniotomy, fosaprepitant is more effective than ondansetron in increasing the rate of complete response and decreasing the incidence of vomiting at 24 and 48 hours postoperatively.

Wenzell CM, Berger MJ, Blazer MA, et al. Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy. *Support Care Cancer.* 2013;21(10):2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either

ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC)., METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data., RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR., CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

Yu Z, Liu W, Wang L, et al. The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicenter, randomized, double-blind, parallel, comparative clinical trial. *Support Care Cancer*. 2009;17(1):99-102.

PURPOSE: This clinical trial was conducted to evaluate the efficacy and safety of Palonosetron in preventing chemotherapy-induced vomiting (CIV) among the Chinese cancer patients., PATIENTS AND METHODS: Two hundred and forty patients were scheduled to be enrolled and randomized to receive a single intravenous dose of palonosetron 0.25 mg, or granisetron 3 mg, 30 min before receiving highly emetogenic chemotherapy. The primary efficacy endpoint was the complete response (CR) rate for acute CIV (during the 0-24-h interval after chemotherapy). Secondary endpoints included the CR rates for delayed CIV (more than 24 h after chemotherapy)., RESULTS: Two hundred and eight patients were accrued and received study medication. CR rates for acute CIV were 82.69% for palonosetron and 72.12% for granisetron, which demonstrated that palonosetron was not inferior to granisetron in preventing acute CIV. Comparisons of CR rates for delayed CIV yielded no statistical difference between palonosetron and granisetron groups and did not reveal non-inferiority of palonosetron to granisetron. Adverse events were mostly mild to moderate, with quite low rates among the two groups., CONCLUSIONS: A single dose (0.25 mg) of palonosetron is not inferior to a single dose (3 mg) of granisetron in preventing CIV and possesses an acceptable safety profile in the Chinese population.

Add-on Trials

Aapro M, Karthaus M, Schwartzberg L, et al. NEPA, a fixed oral combination of netupitant and palonosetron, improves control of chemotherapy-induced nausea and vomiting

(CINV) over multiple cycles of chemotherapy: results of a randomized, double-blind, phase 3 trial versus oral palonosetron. *Support Care Cancer.* 2017;25(4):1127-1135.

PURPOSE: Antiemetic guidelines recommend co-administration of targeted prophylactic medications inhibiting molecular pathways involved in emesis. NEPA is a fixed oral combination of a new NK1 receptor antagonist (RA), netupitant (NETU 300 mg), and palonosetron (PALO 0.50 mg), a pharmacologically distinct 5-HT3 RA. NEPA showed superior prevention of chemotherapy-induced nausea and vomiting (CINV) compared with oral PALO in a single chemotherapy cycle; maintenance of efficacy/safety over continuing cycles is the objective of this study., METHODS: This study is a multinational, double-blind study comparing a single oral dose of NEPA vs oral PALO in chemotherapy-naive patients receiving anthracycline/cyclophosphamide-based chemotherapy along with dexamethasone 12 mg (NEPA) or 20 mg (PALO) on day 1. The primary efficacy endpoint was delayed (25-120 h) complete response (CR: no emesis, no rescue medication) in cycle 1. Sustained efficacy was evaluated during the multicycle extension by calculating the proportion of patients with overall (0-120 h) CR in cycles 2-4 and by assessing the probability of sustained CR over multiple cycles., RESULTS: Of 1455 patients randomized, 1286 (88 %) participated in the multiple-cycle extension for a total of 5969 cycles; 76 % completed >=4 cycles. The proportion of patients with an overall CR was significantly greater for NEPA than oral PALO for cycles 1-4 (74.3 vs 66.6 %, 80.3 vs 66.7 %, 83.8 vs 70.3 %, and 83.8 vs 74.6 %, respectively; p <= 0.001 each cycle). The cumulative percentage of patients with a sustained CR over all 4 cycles was also greater for NEPA (p < 0.0001). NEPA was well tolerated over cycles., CONCLUSIONS: NEPA, a convenient, guideline-consistent, fixed antiemetic combination is effective and safe over multiple cycles of chemotherapy.

Abdel-Malek R, Abbas N, Shohdy Kyrillus S, et al. Addition of 3-day aprepitant to ondansetron and dexamethasone for prophylaxis of chemotherapy-induced nausea and vomiting among patients with diffuse large B cell lymphoma receiving 5-day cisplatin-based chemotherapy. *J Egypt Natl Canc Inst.* 2017;29(3):155-158.

BACKGROUND: Neurokinin-1 receptor antagonists, such as aprepitant are currently emerging as powerful prophylactic agents for chemotherapy-induced nausea and vomiting (CINV). Therefore, it is important to adjust the anti-emetic regimens based on personal risk factors of the patient, duration of the chemotherapy regimen and cost-effectiveness., PURPOSE: To determine the efficacy of the 3-day aprepitant along with ondansetron and dexamethasone in controlling CINV in patients with large B cell lymphoma receiving multiday-cisplatin regimen chemotherapy., METHODS: This is a pilot prospective cross-over trial. Patients were allocated to either aprepitant 125mg on day 1 and 80mg on days 2 & 3 or placebo in the first 2 cycles, with crossover to the opposite treatment in the 3rd and 4th cycles. The primary end point was complete response (CR) of both acute (days 1-5) and delayed (days 6-8) CINV. CR means neither to develop emetic episodes nor to use rescue anti-emetics medication., RESULTS: Twelve of the 15 patients recruited for the study were fully evaluable and completed 4 cycles of ESHAP regimen with a

total of 48 cycles given. In the cycles with aprepitant and those without the CR were 83.3% and 0% respectively (p<0.05). Patients receiving aprepitant in the first 2 cycles recorded less nausea in subsequent cycles that were given without aprepitant. This was not statistically significant., CONCLUSION: This triple anti-emetic regimen showed efficacy in controlling the multi-day cisplatin-induced nausea and vomiting. Further randomized controlled trials are needed to compare between 3-day and 7-day aprepitant for multi-day cisplatin regimens.Copyright © 2017. Production and hosting by Elsevier B.V.

Albany C, Brames MJ, Fausel C, Johnson CS, Picus J, Einhorn LH. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a Hoosier Oncology Group study. *J Clin Oncol.* 2012;30(32):3998-4003.

PURPOSE: Aprepitant, a 5-HT3 receptor antagonist (5HT3-RA), and dexamethasone are standard antiemetic therapy for prevention of single-day, cisplatin-induced nausea and vomiting. We conducted a double-blind, placebo-controlled phase III cross-over study that compared aprepitant to placebo combined with standard antiemetic prophylaxis (a 5HT3-RA and dexamethasone) in patients receiving 5 days of cisplatin combination chemotherapy for testicular cancer., PATIENTS AND METHODS: Patients receiving two consecutive identical courses of a 5-day cisplatin-based chemotherapy were randomly assigned to aprepitant 125 mg on day 3 and 80 mg per day on days 4 through 7 or to placebo with the initial course and crossover to the opposite treatment with the second course. The primary objective was complete response (CR). Secondary end points were emetic episodes (acute and delayed), nausea measurement based on a visual analog scale (VAS), and patient-stated preference after the second study cycle., RESULTS: In all, 71 patients were screened for the study and 69 were evaluable. Thirty-five patients were randomly assigned to receive aprepitant and 34 to receive placebo for the first course. Forty-two percent achieved CR with aprepitant compared with 13% with placebo (P < .001). Eleven patients (16.2%) had at least one emetic episode during the aprepitant cycle versus 32 patients (47.1%) with placebo. Thirty-eight patients preferred the aprepitant cycle whereas 11 preferred placebo (P < .001). There was no statistical difference in VAS for nausea, but it was numerically superior with aprepitant. There was no toxicity with aprepitant compared with placebo., CONCLUSION: There was a significant improvement in CR rate with aprepitant combined with a 5HT3-RA and dexamethasone. Patient preference strongly favored the aprepitant cycle.

Badar T, Cortes J, Borthakur G, et al. Phase II, open label, randomized comparative trial of ondansetron alone versus the combination of ondansetron and aprepitant for the prevention of nausea and vomiting in patients with hematologic malignancies receiving regimens containing high-dose cytarabine. *BioMed Res Int.* 2015;2015:497597.

Background. Aprepitant is a P/neurokinin-1 receptor antagonist approved for the prevention of CINV in moderate emetic risk chemotherapy. We explored its effectiveness in patients with leukemia receiving cytarabine-based chemotherapy. Methods. Patients were randomized to ondansetron (OND) 8mg IV 30 minutes before cytarabine followed by 24mg IV continuous infusion daily until 6-12 hours after the last dose of chemotherapy alone or with aprepitant (APREP) oral 125mg 6-12hrs before chemotherapy and 80mg daily until 1 day after the last dose of chemotherapy. Results. Forty-nine patients were enrolled in each arm; 42 in OND and 41 in OND + APREP arm were evaluable for efficacy. The ORR with OND + APREP was 80% compared to 67% with OND alone (P = 0.11). On days 6 and 7, higher proportion of patients treated with OND + APREP were free from nausea (74%, 74% versus 68%, 67%; P = 0.27 and 0.18, resp.). Requirement of rescue medications on days 2 and 3 was fewer in OND + APREP arm 7% and 5% compared to 21% and 16% in the OND arm, respectively (P = 0.06 and P = 0.07). Conclusions. There was a trend for overall improvement in emesis with ondansetron plus aprepitant. The potential benefit of this approach with specific chemotherapy combinations remains to be determined.

Bakhshi S, Batra A, Biswas B, Dhawan D, Paul R, Sreenivas V. Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: a randomized, double-blind, placebo-controlled trial. *Support Care Cancer.* 2015;23(11):3229-3237.

BACKGROUND: Aprepitant, a neurokinin-1 receptor antagonist, in combination with 5 HT-3 antagonist and dexamethasone is recommended in adults receiving moderately and highly emetogenic chemotherapy to reduce chemotherapy-induced vomiting (CIV). Data for use of aprepitant in children is limited and hence aprepitant is not recommended by Pediatric Oncology Group of Ontario guidelines for prevention of CIV in children <12 years., METHODS: A randomized, double-blind, placebo-controlled trial was conducted at a single center in chemotherapy naive children (5-18 years) receiving highly emetogenic chemotherapy. All patients received intravenous ondansetron (0.15 mg/kg) and dexamethasone (0.15 mg/kg) prior to chemotherapy followed by oral ondansetron and dexamethasone. Patients randomly assigned to aprepitant arm received oral aprepitant (15-40 kg = days 1-3, 80 mg; 41-65 kg = day 1, 125 mg and days 2-3, 80 mg) 1 h before chemotherapy. Control group received placebo as add-on therapy. Primary outcome measure was the incidence of acute moderate to severe vomiting, which was defined as more than two vomiting episodes within 24 h after the administration of the first chemotherapy dose until 24 h after the last chemotherapy dose in the block. Complete response (CR) was defined as absence of vomiting and retching during the specified phase., RESULTS: Of the 96 randomized patients, three were excluded from analysis; 93 patients were analyzed (50 in aprepitant arm and 43 in placebo arm). Acute moderate and severe vomiting was reported in 72 % patients receiving placebo and 38 % patients receiving aprepitant (p = 0.001). Complete response rates during acute phase were significantly higher in aprepitant arm (48 vs. 12 %, p < 0.001). No major adverse effects were reported by patients/guardians., CONCLUSIONS: This double-blind, randomized, placebo-controlled trial

shows that aprepitant significantly decreases the incidence of CIV during acute phase when used as an add-on drug with ondansetron and dexamethasone in children receiving highly emetogenic chemotherapy.

Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. *Pediatr Blood Cancer.* 2009;52(2):242-247.

BACKGROUND: The neurokinin-1 receptor antagonist aprepitant, plus a 5HT3 antagonist and corticosteroid is well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in adults but has not been formally assessed in adolescents., PROCEDURE: Patients age 11-19 years old receiving emetogenic chemotherapy were randomized 2:1 to aprepitant triple therapy (aprepitant [A] 125 mg p.o., dexamethasone [D] 8 mg p.o., and ondansetron [O] 0.15 mg/kg i.v. t.i.d. day 1; A 80 mg, D 4 mg, and O 0.15 mg/kg t.i.d. day 2; A 80 mg and D 4 mg day 3; and D 4 mg day 4) or a control regimen (D 16 mg and O 0.15 mg/kg t.i.d. day 1; D 8 mg and O 0.15 mg/kg t.i.d. day 2; and D 8 mg days 3 and 4). The primary endpoint was the difference in drug-related adverse events during and for 14 days following treatment. Efficacy and aprepitant pharmacokinetics were assessed., RESULTS: Baseline characteristics were similar between aprepitant (N = 28) and control (N = 18) groups. Febrile neutropenia was more frequent in the aprepitant group (25% vs. 11.1%). Complete response (CR) rates were 35.7% for aprepitant triple therapy versus 5.6% for the control group. Mean plasma aprepitant AUC(0-24 hr) and C(max) on day 1 and mean trough concentrations on days 2 and 3 were consistently lower compared to historical data obtained from healthy adults; however, the differences were not clinically significant., CONCLUSION: Aprepitant triple therapy was generally well tolerated; CR were greater with aprepitant, although not statistically significant. Pharmacokinetics suggest that the adult dosing regimen is appropriate for adolescents.

Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. *Ann Oncol.* 2014;25(7):1340-1346.

BACKGROUND: NEPA is a novel oral fixed-dose combination of netupitant (NETU), a new highly selective neurokinin-1 (NK1) receptor antagonist (RA) and palonosetron (PALO), a pharmacologically and clinically distinct 5-hydroxytryptamine type 3 (5-HT3) RA. This study was designed to determine the appropriate clinical dose of NETU to combine with PALO for evaluation in the phase 3 NEPA program., PATIENTS AND METHODS: This randomized, double-blind, parallel group study in 694 chemotherapy naive patients undergoing cisplatin-based chemotherapy for solid tumors compared three different oral doses of NETU (100, 200, and 300 mg) + PALO 0.50 mg with oral PALO 0.50 mg, all given on day 1. A standard 3-day aprepitant (APR) + IV ondansetron (OND) 32 mg regimen was included as an exploratory arm. All patients received oral dexamethasone on days 1-4. The primary efficacy endpoint was complete

response (CR: no emesis, no rescue medication) during the overall (0-120 h) phase., RESULTS: All NEPA doses showed superior overall CR rates compared with PALO (87.4%, 87.6%, and 89.6% for NEPA100, NEPA200, and NEPA300, respectively versus 76.5% PALO; P < 0.050) with the highest NEPA300 dose studied showing an incremental benefit over lower NEPA doses for all efficacy endpoints. NEPA300 was significantly more effective than PALO and numerically better than APR + OND for all secondary efficacy endpoints of no emesis, no significant nausea, and complete protection (CR plus no significant nausea) rates during the acute (0-24 h), delayed (25-120 h), and overall phases. Adverse events were comparable across groups with no dose response. The percent of patients developing electrocardiogram changes was also comparable., CONCLUSIONS: Each NEPA dose provided superior prevention of chemotherapy-induced nausea and vomiting (CINV) compared with PALO following highly emetogenic chemotherapy; however, NEPA300 was the best dose studied, with an advantage over lower doses for all efficacy endpoints. The combination of NETU and PALO was well tolerated with a similar safety profile to PALO and APR + OND.

Hu Z, Cheng Y, Zhang H, et al. Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial. *Support Care Cancer.* 2014;22(4):979-987.

PURPOSE: Aprepitant, an oral neurokinin-1 receptor antagonist, has demonstrated improved control of chemotherapy-induced nausea and vomiting (CINV) in previous studies. This is the first phase III study to evaluate the efficacy and tolerability of aprepitant in patients receiving highly emetogenic chemotherapy (HEC) in Asian countries., METHODS: This multicenter, double-blind, placebo-controlled trial assessed the prevention of CINV during the acute phase (AP), delayed phase (DP), and overall phase (OP). Patients receiving HEC were randomized to either an aprepitant group (day 1, aprepitant 125 mg; days 2-3, aprepitant 80 mg) or a standard therapy group (days 1-3, placebo). Both groups received intravenous granisetron and oral dexamethasone. The primary end point was complete response (CR; no emesis and no use of rescue therapy) during the OP., RESULTS: Of the 421 randomized patients, 411 (98%) were assessable for efficacy; 69.6% (142/204) and 57.0% (118/207) of patients reported CR during the OP in the aprepitant and standard therapy groups, respectively (P = 0.007). CR rates in the aprepitant group were higher during the DP (74.0% vs. 59.4%, P = 0.001) but were similar during the AP (79.4% vs. 79.3%, P = 0.942). Toxicity and adverse events were comparable in both groups., CONCLUSIONS: The addition of aprepitant to standard antiemetic treatment regimens for Chinese patients undergoing HEC provided superior CINV prevention and was well tolerated.

Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16(4):385-394.

BACKGROUND: Oral aprepitant, a neurokinin-1 receptor antagonist, is recommended in combination with other anti-emetic agents for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy in adults, but its efficacy and safety in paediatric patients are unknown. We did this phase 3 trial to examine the safety and efficacy of such treatment in children., METHODS: In this final analysis of a phase 3, randomised, multicentre, double-blind study, patients aged 6 months to 17 years with a documented malignancy who were scheduled to receive either moderately or highly emetogenic chemotherapy were randomly assigned with an interactive voice response system to an age-based and weight-based blinded regimen of aprepitant (125 mg for ages 12-17 years; 3.0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12-17 years; 2.0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3, or placebo plus ondansetron on day 1 followed by placebo on days 2 and 3; addition of dexamethasone was allowed. Randomisation was stratified according to patient age, planned use of chemotherapy associated with very high risk of emetogenicity, and planned use of dexamethasone as an anti-emetic. Ondansetron was dosed per the product label for paediatric use or local standard of care. The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25-120 h (delayed phase) after initiation of emetogenic chemotherapy. Efficacy and safety analyses were done with all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01362530., FINDINGS: Between Sept 22, 2011, and Aug 16, 2013, 307 patients were randomly assigned at 49 sites in 24 countries to either the aprepitant group (155 patients) or to the control group (152 patients). Three patients in the aprepitant group and two in the control group did not receive study medication, and thus were excluded from analyses. 77 (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase ($p<0.0001$). The most common grade 3-4 adverse events were febrile neutropenia (23 [15%] of 152 in the aprepitant group vs 21 [14%] of 150 in the control group), anaemia (14 [9%] vs 26 [17%]), and decreased neutrophil count (11 [7%] vs 17 [11%]). The most common serious adverse event was febrile neutropenia (23 [15%] patients in the aprepitant group vs 22 [15%] in the control group)., INTERPRETATION: Addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients being treated with moderately or highly emetogenic chemotherapy., FUNDING: Merck & Co., Inc.

Kim JE, Jang J-S, Kim J-W, et al. Efficacy and safety of aprepitant for the prevention of chemotherapy-induced nausea and vomiting during the first cycle of moderately emetogenic chemotherapy in Korean patients with a broad range of tumor types. *Support Care Cancer.* 2017;25(3):801-809.

PURPOSE: This study evaluated the efficacy and safety of a 3-day aprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) during the first cycle of non-anthracycline plus cyclophosphamide (AC)-based moderately emetogenic chemotherapy (MEC) based on government guidelines in Korean patients., METHODS: This multicenter, randomized, double-blind, phase IV trial (NCT01636947) enrolled adult South Korean patients with a broad range of tumor types who were scheduled to receive a single dose of >=1 MEC agent. Patients were randomized to a 3-day regimen of aprepitant (aprepitant regimen) or placebo (control regimen) on top of ondansetron plus dexamethasone. The primary and key secondary efficacy endpoints were the proportions of subjects who achieved no vomiting and complete response (CR) during the overall phase., RESULTS: Of the 494 randomized subjects, 480 were included in the modified intent-to-treat population. Response rates for no vomiting and CR in the overall phase were numerically higher for the aprepitant regimen compared with the control regimen groups, but failed to reach statistical significance (no vomiting 77.2 vs 72.0%; p = 0.191; CR 73.4 vs 70.4%; p = 0.458). Both the aprepitant and control regimens were generally well tolerated., CONCLUSION: A 3-day aprepitant regimen was numerically better but not statistically superior to a control regimen with respect to the achievement of no vomiting or CR during the overall phase in a non-AC MEC Korean population based on government reimbursement guidelines., TRIAL REGISTRATION: ClinicalTrials.gov NCT01636947 (https://clinicaltrials.Gov/ct2/show/NCT01636947).

Nasu R, Nannya Y, Kurokawa M. A randomized controlled study evaluating the efficacy of aprepitant for highly/moderately emetogenic chemotherapies in hematological malignancies. *Int J Hematol.* 2015;101(4):376-385.

Chemotherapy-induced nausea and vomiting (CINV) is a serious complication of treatments of hematological malignancies. Although aprepitant, an NK1 receptor antagonist, has been shown to control CINV in highly emetogenic therapies for solid tumors, the antiemetic effect of this agent in hematological chemotherapies is not well established. In this randomized controlled trial, we examined the additional effect of aprepitant in combination with conventional 5HT3 blocker-based prophylaxis for CINV in highly or moderately emetic chemotherapies for hematological malignancies (n = 41). The complete response rate, defined as no emetic episodes and no salvage treatments, was significantly higher in the aprepitant arm than the control arm (82 versus 47 %, p = 0.026), with no increase in severe adverse effects. However, the difference of nausea, measured with visual analog scale, and of oral intake impairment was moderate, which suggests insufficiency of blocking NK receptor for these events. Furthermore, sub-group analysis revealed that merit of aprepitant addition depends on treatment regimens. Our results indicate the overall advantage of applying aprepitant in the control of CINV in hematological malignancies and the need for further refinement of anti-CINV strategies, including stratification according to regimen.

Nishimura J, Satoh T, Fukunaga M, et al. Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based

chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. *Eur J Cancer.* 2015;51(10):1274-1282.

INTRODUCTION: The oral neurokinin-1 antagonist aprepitant is recommended in several guidelines for preventing chemotherapy-induced nausea & vomiting (CINV) due to highly emetogenic cancer chemotherapy. Little is known about the feasibility and safety of aprepitant in patients treated with oxaliplatin., METHODS: In this multicentre, open label, randomised, phase 3 trial, we recruited patients with colorectal cancer who underwent an oxaliplatin-based chemotherapy. Patients were centrally randomised in a 1:1 ratio to the control group (5-HT3-receptor antagonist+dexamethasone) or aprepitant group (5-HT3-receptor antagonist+dexamethasone+aprepitant or fosaprepitant) in the first course. All patients were treated with aprepitant/fosaprepitant therapy in the second course. The primary end-point was the proportion of patients with no emesis., RESULTS: A total of 413 patients entered this clinical trial from 25 centres in Japan. Significantly more patients in the aprepitant group achieved no vomiting overall and delayed phase than those in the control group (95.7% versus 83.6%, and 95.7% versus 84.7%, respectively). The aprepitant group also had statistically significantly higher percentages of no significant nausea, complete response and complete protection than the control group overall. In the control group, the percentages of no vomiting were higher in the second cycle than in the first cycle. The incidence of vomiting occurred day 7 or later was significantly higher in the control group compared with the aprepitant group. Other adverse events were not significant between the groups., CONCLUSION: The aprepitant therapy was more effective than the control therapy for prevention of CINV in colorectal cancer patients receiving an oxaliplatin-based regimen.

Rapoport B, Chua D, Poma A, Arora S, Wang Y, Fein LE. Study of rolapitant, a novel, long-acting, NK-1 receptor antagonist, for the prevention of chemotherapy-induced nausea and vomiting (CINV) due to highly emetogenic chemotherapy (HEC). *Support Care Cancer.* 2015;23(11):3281-3288.

PURPOSE: Rolapitant is a novel, long-acting neurokinin-1 (NK-1) receptor antagonist. This study evaluated the safety and efficacy of four different doses of rolapitant for prevention of chemotherapy-induced nausea and vomiting (CINV) due to highly emetogenic chemotherapy (HEC)., METHODS: This randomized, double-blind, active-controlled, global study was conducted in patients receiving cisplatin-based chemotherapy >=70 mg/m(2). Patients received a 9, 22.5, 90, or 180 mg oral dose of rolapitant or placebo with ondansetron and dexamethasone on day 1 of chemotherapy. The primary end point was complete response (CR; no emesis and no use of rescue medication) in the overall (0 to 120 h) phase of cycle 1. Other assessments were CR in delayed (24-120 h) and acute (0-24 h) phases, no emesis, no significant nausea, and no nausea., RESULTS: Four hundred fifty-four patients were randomized. All doses of rolapitant improved CR with the greatest benefit observed with rolapitant 180 mg vs. active control in the overall phase (62.5 and 46.7 %, p = 0.032) and in the acute (87.6 vs. 66.7 %, p = 0.001) and delayed (63.6 vs. 48.9 %, p = 0.045) phases. Rates for no emesis and no significant nausea were significantly (p <

0.05) higher with rolapitant 180 mg vs. active control in the overall, acute, and delayed phases. Treatment-related adverse events were largely considered related to the chemotherapy and included constipation, headache, fatigue, and dizziness which were mostly mild or moderate and were similar across treatment groups., CONCLUSION: All doses of rolapitant were well tolerated and showed greater CR rates than active control. Rolapitant 180 mg demonstrated significant clinical efficacy for preventing CINV in the overall, delayed, and acute phases for patients receiving HEC.

Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. *Lancet Oncol.* 2015;16(9):1079-1089.

BACKGROUND: Highly emetogenic chemotherapy induces emesis in almost all patients in the absence of prophylaxis. Guidelines recommend use of a neurokinin-1 (NK-1) receptor antagonist in conjunction with a 5-HT3 receptor antagonist and corticosteroid in patients receiving highly emetogenic chemotherapy. We aimed to assess rolapitant, an NK-1 receptor antagonist, for prevention of chemotherapy-induced nausea and vomiting in patients with cancer after administration of cisplatin-based highly emetogenic chemotherapy., METHODS: We conducted two global, randomised, double-blind, active-controlled, phase 3 trials (HEC-1 and HEC-2) at 155 cancer centres (76 in HEC-1 and 79 in HEC-2) in 26 countries (17 in HEC-1 and 14 in HEC-2). We enrolled patients with cancer aged 18 years or older, who had not previously been treated with cisplatin, with a Karnofsky performance score of 60 or higher, and a predicted life expectancy of 4 months or longer. We used an interactive web-based randomisation system to randomly assign patients to treatment. Patients were stratified by sex and randomly allocated to either oral rolapitant (180 mg dose; rolapitant group) or a placebo that was identical in appearance (active control group) about 1-2 h before administration of highly emetogenic chemotherapy. All patients received granisetron (10 mug/kg intravenously) and dexamethasone (20 mg orally) on day 1, and dexamethasone (8 mg orally) twice daily on days 2-4. Every cycle was a minimum of 14 days. In up to five subsequent cycles, patients were allowed to receive the same study drug they were assigned in cycle 1, unless removed at the clinician's discretion. Patients could also choose to leave the study at any point. Efficacy analysis was done in the modified intention-to-treat population (comprising all patients who received at least one dose of study drug at a cancer centre compliant with Good Clinical Practice [GCP]). The primary endpoint was the proportion of patients achieving a complete response (no emesis or use of rescue medication) in the delayed phase (>24-120 h after initiation of chemotherapy) in cycle 1. These studies are registered with ClinicalTrials.gov, numbers NCT01499849 and NCT01500213. Both studies have been completed., FINDINGS: Between Feb 21, 2012, and March 12, 2014, 532 patients in HEC-1 and 555 patients in HEC-2 were randomly assigned to treatment. 526 patients in HEC-1 (264 rolapitant and 262 active control) and 544 in HEC-2 (271 rolapitant and 273 active control) received at least one dose of study drug at a GCP-compliant site and were included in the

modified intention-to-treat population. A significantly greater proportion of patients in the rolapitant group had complete responses in the delayed phase than did patients in the active control group (HEC-1: 192 [73%] vs 153 [58%]; odds ratio 1.9, 95% CI 1.3-2.7; p=0.0006; HEC-2: 190 [70%] vs 169 [62%]; 1.4, 1.0-2.1; p=0.0426; pooled studies: 382 [71%] vs 322 [60%]; 1.6, 1.3-2.1; p=0.0001). The incidence of adverse events was similar across treatment groups. The most commonly reported treatment-related treatment-emergent adverse events in the rolapitant versus active control groups were headache (three [<1%] vs two [<1%]), hiccups (three [<1%] vs four [<1%]), constipation (two [<1%] vs three [<1%]), and dyspepsia (two [<1%] vs three [<1%]). For cycle 1, the most common grade 3-5 adverse events in patients allocated rolapitant versus active control were neutropenia (HEC-1: nine [3%] vs 14 [5%]; HEC-2: 16 [6%] vs 14 [5%]), anaemia (HEC-1: one [<1%] vs one [<1%]; HEC-2: seven [3%] vs two [<1%]), and leucopenia (HEC-1: six [2%] vs two [<1%]; HEC-2: two [<1%] vs two [<1%]). No serious treatment-emergent adverse events were treatment related, and no treatment-related treatment-emergent adverse events resulted in death., INTERPRETATION: Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone is well-tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the at-risk period (120 h) after admin stration of highly emetogenic cisplatin-based chemotherapy., FUNDING: TESARO, Inc.

Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. *Support Care Cancer.* 2010;18(4):423-431.

PURPOSE: Aprepitant was shown previously to be effective for prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately emetogenic chemotherapy (MEC) in breast cancer patients receiving an anthracycline and cyclophosphamide (AC)-based regimen. This study assessed aprepitant in patients receiving a broad range of MEC regimens with a variety of tumor types., METHODS: This phase III, randomized, gender-stratified, double-blind trial enrolled patients with confirmed malignancies, naive to MEC or highly emetogenic chemotherapy, who were scheduled to receive a single dose of at least one MEC agent. Patients received an aprepitant triple-therapy regimen (aprepitant, ondansetron, and dexamethasone) or a control regimen (ondansetron and dexamethasone) administered orally. Primary and key secondary efficacy endpoints were proportions of patients with no vomiting and complete response (no vomiting and no rescue medication), respectively, during the 120 h post-chemotherapy., RESULTS: Of 848 randomized patients, 77% were female, and 52% received non-AC-based antineoplastic regimens. Significantly, more patients in the aprepitant group achieved no vomiting and complete response, regardless of whether they received AC or non-AC regimens, in the 120 h after chemotherapy. Overall, the incidences of adverse events were generally similar in the aprepitant (62.8%) and control groups (67.2%)., CONCLUSIONS: The aprepitant regimen provided superior efficacy in the treatment of CINV in a broad range of

patients receiving MEC (non-AC or AC) in both no vomiting and complete response endpoints. Aprepitant was generally well tolerated. These results show the benefit of including aprepitant as part of the standard antiemetic regimen for cancer patients receiving MEC.

Schmitt T, Goldschmidt H, Neben K, et al. Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: results of a randomized, placebo-controlled phase III trial. *J Clin Oncol.* 2014;32(30):3413-3420.

PURPOSE: The optimal regimen to prevent chemotherapy-induced nausea and vomiting (CINV) for patients undergoing high-dose chemotherapy and autologous stem-cell transplantation (ASCT) is unclear. To evaluate the effect of aprepitant in addition to a standard regimen, we conducted this randomized, placebo-controlled phase III trial., PATIENTS AND METHODS: Patients with multiple myeloma were randomly assigned at a one-to-one ratio to receive either aprepitant (125 mg orally on day 1 and 80 mg orally on days 2 to 4), granisetron (2 mg orally on days 1 to 4), and dexamethasone (4 mg orally on day 1 and 2 mg orally on days 2 to 3) or matching placebo, granisetron (2 mg orally on days 1 to 4), and dexamethasone (8 mg orally on day 1 and 4 mg orally on days 2 to 3). Melphalan 100 mg/m(2) was administered intravenously on days 1 to 2. ASCT was performed on day 4. The primary end point (complete response) was defined as no emesis and no rescue therapy within 120 hours of melphalan administration. Quality of life was assessed by modified Functional Living Index-Emesis (FLIE) questionnaire on days -1 and 6., RESULTS: Overall, 362 patients were available for the efficacy analysis (181 in each treatment arm). Significantly more patients receiving aprepitant reached the primary end point (58% v 41%; odds ratio [OR], 1.92; 95% CI, 1.23 to 3.00; P = .0042). Absence of major nausea (94% v 88%; OR, 2.37; 95% CI, 1.09 to 5.15; P = .026) and emesis (78% v 65%; OR, 1.99; 95% CI, 1.25 to 3.18; P = .0036) within 120 hours was increased by aprepitant. Mean total FLIE score (+/- standard deviation) was 114 +/- 18 for aprepitant and 106 +/- 26 for placebo (P < .001)., CONCLUSION: The addition of aprepitant resulted in significantly less CINV and had a positive effect on quality of life.

Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16(9):1071-1078.

BACKGROUND: Chemotherapy-induced nausea and vomiting is a common side-effect of many antineoplastic regimens and can occur for several days after treatment. We aimed to assess the neurokinin-1 receptor antagonist rolapitant, in combination with a serotonin (5-HT3) receptor antagonist and dexamethasone, for the prevention of chemotherapy-induced nausea and vomiting in patients with cancer after administration of moderately emetogenic chemotherapy or regimens containing an anthracycline and cyclophosphamide., METHODS: We conducted a

global, randomised, double-blind, active-controlled, phase 3 study at 170 cancer centres in 23 countries. We included patients with cancer aged 18 years or older, who had not received moderately or highly emetogenic chemotherapy before, with a Karnofsky performance score of 60 or higher, and a predicted life expectancy of 4 months or longer. We used an interactive web-based randomisation system to randomly allocate patients to receive either oral rolapitant (one 180 mg dose; rolapitant group) or a placebo that was identical in appearance (active control group) 1-2 h before administration of moderately emetogenic chemotherapy. Patients were stratified by sex. All patients also received granisetron (2 mg orally) and dexamethasone (20 mg orally) on day 1 (except for patients receiving taxanes as part of moderately emetogenic chemotherapy, who received dexamethasone according to the package insert) and granisetron (2 mg orally) on days 2-3. Every cycle was a minimum of 14 days. In up to five subsequent cycles, patients received the same study drug they were assigned in cycle 1, unless they chose to leave the study or were removed at the treating clinician's discretion. Efficacy analysis was done in the modified intention-to-treat population (comprising all patients who received at least one dose of study drug at a study site compliant with Good Clinical Practice [GCP]). The primary endpoint was the proportion of patients achieving a complete response (defined as no emesis or use of rescue medication) in the delayed phase (>24-120 h after initiation of chemotherapy) in cycle 1. This study is registered with ClinicalTrials.gov, number NCT01500226. The study has been completed., FINDINGS: Between March 5, 2012, and Sept 6, 2013, 1369 patients were randomised to receive either rolapitant (n=684) or active control (n=685). 666 patients in each group received at least one dose of study drug at a GCP-compliant site and were included in the modified intention-to-treat population. A significantly greater proportion of patients receiving rolapitant had complete responses in the delayed phase than did those receiving active control (475 [71%] vs 410 [62%]; odds ratio 1.6, 95% CI 1.2-2.0; p=0.0002). The incidence of adverse events was similar in the rolapitant and control groups, with the most frequently reported treatment-related treatment-emergent adverse events being fatigue, constipation, and headache. For cycle 1, the most common grade 3-4 adverse event in the rolapitant versus active control groups was neutropenia (32 [5%] vs 23 [3%] patients). No serious adverse event was treatment-related, and no treatment-related treatment-emergent adverse event resulted in death., INTERPRETATION: Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone is well tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the 5-day (0-120 h) at-risk period after administration of moderately emetogenic chemotherapy or regimens containing an anthracycline and cyclophosphamide., FUNDING: TESARO, Inc.

Sinha AC, Singh PM, Williams NW, Ochroch EA, Goudra BG. Aprepitant's prophylactic efficacy in decreasing postoperative nausea and vomiting in morbidly obese patients undergoing bariatric surgery. *Obes Surg.* 2014;24(2):225-231.

BACKGROUND: Postoperative nausea and vomiting is a major cause of patient dissatisfaction towards surgery. For bariatric surgery, increased vomiting/retching is detrimental to surgical anastomosis. The present study evaluated the efficacy of aprepitant (neurokinin-1 inhibitor) as a prophylactic antiemetic in morbidly obese patients for laparoscopic bariatric surgery., METHODS: After institutional review board approval, 125 morbidly obese patients were recruited into this double-blind placebo-controlled trial. On random division, the patients received a tablet of aprepitant (80 mg) in group A, or a similar-appearing placebo in group P, an hour prior to surgery. All patients received intravenous ondansetron (4 mg) intraoperatively. Postoperatively, the patients were evaluated for nausea and vomiting by a blinded evaluator at 30 min, 1, 2, 6, 24, 48, and 72 h., RESULTS: Both groups were evenly distributed for age, body mass index, type, and length of surgery. Cumulative incidence of vomiting at 72 h was significantly lower in group A (3%) compared to group P (15%; p=0.021). Odds ratio for vomiting in group P compared to group A was 5.47 times. On Kaplan-Meier plot, time to first vomiting was also significantly delayed in group A (p=0.019). A higher number of patients showed complete absence of nausea or vomiting in group A compared to group P (42.18 vs. 36.67%). On the other hand, nausea scores were unaffected by aprepitant, and no significant difference between groups was found at any of the measured time points., CONCLUSIONS: In morbidly obese patients undergoing laparoscopic bariatric surgery, addition of aprepitant to ondansetron can significantly delay vomiting episodes simultaneously lowering the incidence of postoperative vomiting.

Song Z, Wang H, Zhang H, Zhao K, Zhang M, Yang F. Efficacy and safety of triple therapy with aprepitant, ondansetron, and prednisone for preventing nausea and vomiting induced by R-CEOP or CEOP chemotherapy regimen for non-Hodgkin lymphoma: a phase 2 open-label, randomized comparative trial. *Leukemia Lymphoma.* 2017;58(4):816-821.

We performed a prospective study to investigate the efficacy and safety of triple therapy with aprepitant, ondansetron, and prednisone in non-Hodgkin lymphoma patients receiving R-CEOP or CEOP chemotherapy regimen. All patients were randomly assigned to either an aprepitant regimen (aprepitant plus ondansetron and prednisone), or a control regimen (ondansetron and prednisone) treatment group. For the complete response, the aprepitant group was statistically superior to the control group in the overall study period (76.5% vs. 56.0%; p=.03), as well as in separate analyses of the acute phase (92.2% vs. 78.0%; p=.045), and even more notably in the delayed phase (82.4% vs. 64.0%; p=.037). The overall incidence of adverse events was similar between the two treatment groups (p>.05). The aprepitant regimen was more effective than the control regimen for the prevention of CINV in patients receiving R-CEOP or CEOP regimen and was generally well tolerated.

Svanberg A, Birgegard G. Addition of aprepitant (Emend) to standard antiemetic regimen continued for 7 days after chemotherapy for stem cell transplantation provides significant reduction of vomiting. *Oncology.* 2015;89(1):31-36.

Chemotherapy-induced nausea/vomiting (CINV) is a major problem for patients treated with high-dose chemotherapy (HDCT) conditioning before stem cell transplantation (SCT), both during chemotherapy and afterwards (delayed nausea/vomiting). The standard of care (5-HT3 antagonist and dexamethasone) appears to be ineffective against delayed nausea and vomiting. The objective of this study was to compare standard antiemetic treatment with standard treatment plus prolonged treatment with aprepitant (Emend) until 7 days after the end of chemotherapy in patients treated with HDCT before autologous SCT. Ninety-six patients were randomized to the experiment (EXP) group receiving Emend in addition to standard antiemetics or to the control (CTR) group receiving placebo. Emend or placebo treatment started 1 h before the first HDCT dose for SCT and ended 7 days after HDCT. Thirty-eight patients in the EXP group experienced complete response (no vomiting) compared to 16 patients in the CTR group. There was a significant difference between the EXP (0.63 +/- 2.71) and the CTR (3.72 +/- 4.91) group during 10 days after the end of HDCT (p = 0.001) with regard to the number of vomiting episodes. No difference with regard to days of nausea or in the use of antiemetic rescue was noted between the groups. We conclude that standard antiemetic treatment can be improved by addition of aprepitant continued for 7 days after the end of chemotherapy.

Takahashi T, Hoshi E, Takagi M, Katsumata N, Kawahara M, Eguchi K. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. *Cancer Sci.* 2010;101(11):2455-2461.

Aprepitant is a new neurokinin-1 (NK(1)) receptor antagonist developed as a treatment for chemotherapy-induced nausea and vomiting (CINV). To evaluate the efficacy and safety of aprepitant used in combination with standard therapy (granisetron and dexamethasone), we conducted a multicenter, phase II, placebo-controlled, double-blind, randomized study in Japanese cancer patients who received cancer chemotherapy including cisplatin (>=70mg/m(2)). Aprepitant was administered for 5days. A total of 453 patients were enrolled. In the three study groups, (i) standard therapy, (ii) aprepitant 40/25mg (40mg on day 1 and 25mg on days 2-5) and (iii) aprepitant 125/80mg (125mg on day 1 and 80mg on days 2-5), the percentage of patients with complete response (no emesis and no rescue therapy) was 50.3% (75/149 subjects), 66.4% (95/143 subjects) and 70.5% (103/146 subjects), respectively. This shows that efficacy was significantly higher in the aprepitant 40/25mg and 125/80mg groups than in the standard therapy group (chi(2) test [closed testing procedure]: P=0.0053 and P=0.0004, respectively) and highest in the aprepitant 125/80mg group. The delayed phase efficacy (days 2-5) was similar to the overall phase efficacy (days 1-5), indicating that aprepitant is effective in the delayed phase when standard therapy is not very effective. In terms of safety, aprepitant was generally well tolerated in Japanese cancer patients. (ClinicalTrials.gov number, NCT00212602.)

Yeo W, Mo FKF, Suen JJS, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer

patients receiving moderately emetogenic chemotherapy. *Breast Cancer Res Tr.* 2009;113(3):529-535.

OBJECTIVES: This is a single center, randomized, double-blind placebo-controlled study to evaluate the NK(1)-receptor antagonist, aprepitant, in Chinese breast cancer patients. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy. The secondary objective was to compare the patient-reported quality of life in these two groups of patients., PATIENTS AND METHODS: Eligible breast cancer patients were chemotherapy-naive and treated with adjuvant AC chemotherapy (i.e. doxorubicin 60 mg/m(2) and cyclophosphamide 600 mg/m(2)). Patients were randomly assigned to either an aprepitant-based regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, aprepitant 80 qd) or a control arm which consisted of standard regimen (day 1, ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary, patients quality of life were assessed by self-administered Functional Living Index-Emesis (FLIE)., RESULTS: Of 127 patients randomized, 124 were assessable. For CINV in Cycle 1 AC, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea'. The requirement of rescue medication appears to be lesser in patients treated with the aprepitant-based regimen compared to those with the standard regimen (11% vs. 20%; P = 0.06). Assessment of FLIE revealed that while there was no difference in the nausea domain and the total score between the two groups; however, patients receiving standard antiemetic regimen had significantly worse quality of life in the vomiting domain (mean score [SD] = 23.99 [30.79]) when compared with those who received the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) (P = 0.0002). Both treatments were generally well tolerated. Patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (53.2% vs. 35.5%, P = 0.0468), grade >or= 3 neutropenia (21.0% vs. 45.2, P = 0.0042) and delay in subsequent cycle of chemotherapy (8.1% vs. 27.4%, P = 0.0048)., CONCLUSION: The aprepitant regimen appears to reduce the requirement of rescue medication when compared with the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide, and is associated with a better quality of life during adjuvant AC chemotherapy.

Placebo-controlled Trials

Barrett TW, DiPersio DM, Jenkins CA, et al. A randomized, placebo-controlled trial of ondansetron, metoclopramide, and promethazine in adults. *Am J Emerg Med.* 2011;29(3):247-255.

OBJECTIVES: The objective of the study was to assess whether ondansetron has superior nausea reduction compared with metoclopramide, promethazine, or saline placebo in emergency department (ED) adults., METHODS: This randomized, placebo-controlled, double-blinded superiority trial was intended to enroll a convenience sample of 600 patients. Nausea was evaluated on a 100-mm visual analog scale (VAS) at baseline and 30 minutes after treatment. Patients with a minimum preenrollment VAS of 40 mm were randomized to intravenous ondansetron 4 mg, metoclopramide 10 mg, promethazine 12.5 mg, or saline placebo. A 12-mm VAS improvement in nausea severity was deemed clinically important. We measured potential drug adverse effects at baseline and 30 minutes. Patients received approximately 500 mL of saline hydration during the initial 30 minutes., RESULTS: Of 180 subjects who consented, 163 completed the study. The median age was 32 years (interquartile range, 23-47), and 68% were female. The median 30-minute VAS reductions (95% confidence intervals) and saline volume given for ondansetron, metoclopramide, promethazine, and saline were -22 (-32 to -15), -30 (-38 to -25.5), -29 (-40 to -21), and -16 (-25 to -3), and 500, 500, 500, and 450, respectively. The median 30-minute VAS differences (95% confidence intervals) between ondansetron and metoclopramide, promethazine, and saline were -8 (-18.5 to 3), -7 (-21 to -5.5), and 6 (-7 to 20), respectively. We compared the antiemetic efficacy across all treatments with the Kruskal-Wallis test (P = .16)., CONCLUSIONS: Our study shows no evidence that ondansetron is superior to metoclopramide and promethazine in reducing nausea in ED adults. Early study termination may have limited detection of ondansetron's superior nausea reduction over saline.

Chun HR, Jeon IS, Park SY, Lee SJ, Kang SH, Kim SI. Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial. *Brit J Anaesth.* 2014;112(3):485-490.

BACKGROUND: The aim of this study was to evaluate the efficacy of palonosetron, the latest 5-HT3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) during the first 72 h after operation. METHODS: In this randomized, double-blinded, placebo-controlled study, 204 healthy inpatients who were undergoing elective surgery with general anaesthesia were enrolled. Patients were divided into two groups: the palonosetron group (palonosetron 0.075 mg i.v.; n=102) and the placebo group (normal saline i.v.; n=102). The treatments were given after the induction of anaesthesia. The incidence of nausea, vomiting, severity of nausea, and the use of rescue anti-emetics during the first 72 h after surgery were evaluated. RESULTS: The incidence of PONV was lower in the palonosetron group compared with the placebo group during the 0-24 h (33% vs 47%) and 0-72 h period (33% vs 52%) ($P<0.05$), but not during the 24-72 h postoperative period (6% vs 11%). The incidence of nausea was also significantly lower in the palonosetron group than in the placebo group during the 0-24 and 0-72 h period ($P<0.05$), but not during the 24-72 h postoperative period. However, there were no significant differences in the incidence of vomiting, and the use of rescue anti-emetics between the groups. CONCLUSIONS: Palonosetron 0.075 mg i.v. effectively reduced the

incidence of PONV during the first 72 h after operation, with most of the reduction occurring in the first 24 h.

de Orange FA, Marques J, Flores M, Borges PSGN. Dexamethasone versus ondansetron in combination with dexamethasone for the prophylaxis of postoperative vomiting in pediatric outpatients: a double-blind, randomized, placebo-controlled clinical trial. *Paediatr Anaesth.* 2012;22(9):890-896.

OBJECTIVES: To determine the frequency of postoperative vomiting (POV) in children submitted to outpatient surgery and to compare the efficacy of antiemetic drugs in preventing this complication., BACKGROUND: Nausea and vomiting are common in the immediate postoperative period following anesthetic and surgical procedures. Compared to adults, pediatric patients are more likely to develop postoperative nausea and vomiting, the incidence of which ranges from 8.9% to 42%., METHODS: This double-blind, randomized, placebo-controlled clinical trial included 129 children. The participants were randomized into three prophylactic treatment groups: dexamethasone (n = 43), ondansetron in combination with dexamethasone (n = 44), and placebo (n = 42). The variables studied were the frequency of POV and the incidence of vomiting after the patient had been discharged from hospital, the need for antiemetic rescue therapy in the postanesthesia care unit (PACU), need for hospitalization, and the time the patient remained in the PACU. A significance level of 5% was adopted., RESULTS: Postoperative vomiting occurred in 12.4% of the children, with no statistically significant difference between the groups: 6.8% in the group receiving ondansetron combined with dexamethasone, 14.3% in the placebo group, and 14% in the group that received dexamethasone alone (P = 0.47). Furthermore, no significant difference was found between the groups with respect to the time the children remained in the PACU, and only five patients reported having vomited following discharge from hospital., CONCLUSIONS: The prophylactic use of antiemetic drugs failed to reduce the incidence of POV in pediatric outpatient surgery with a low emetic potential; therefore, routine prophylaxis may be unnecessary.

Ebrahim Soltani AR, Mohammadinasab H, Goudarzi M, et al. Comparing the efficacy of prophylactic p6 acupressure, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery. *Acta Med Iran.* 2011;49(4):208-212.

o compare the efficacy of acupressure wrist bands, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery. Two hundred patients, ASA physical status I or II, aged between 10 and 60 years, undergoing strabismus surgery in Farabi Hospital in 2007-2008 years, were included in this randomized, prospective, double-blind and placebo-controlled study. Group I was the Control, group II received metoclopramide 0.2 mg/kg, group III received ondansetron 0.15 mg/kg iv just before induction, in Group IV acupressure wristbands were applied at the P6 points. Acupressure wrist bands were placed inappropriately in Groups I, II and III. The acupressure wrist bands were applied 30 min prior to the induction of

anesthesia and removed six hours after surgery. Postoperative nausea and vomiting (PONV) was evaluated within 0-2 hours and 2-24 hours after surgery by a blinded observer. Results were analyzed by X(2) test. A P value of < 0.05 was taken as significant. The incidence of PONV was not significantly different in acupressure, metoclopramide and ondansetron during the 24 hours. Acupressure at P6 causes a significant reduction in the incidence of PONV 24 hours after strabismus surgery as well as metoclopramide 0.2 mg/kg and ondansetron 0.15 mg/kg iv for patients aged 10 or more.

Fattahi Z, Hadavi SMR, Sahmeddini MA. Effect of ondansetron on post-dural puncture headache (PDPH) in parturients undergoing cesarean section: a double-blind randomized placebo-controlled study. *J Anesth*. 2015;29(5):702-707.

PURPOSE: One of the most exhausting complications of spinal anesthesia, especially in parturients, is post-dural puncture headache (PDPH). This headache is not responsive to the usual pain killers. Ondansetron is a 5-HT3 receptor antagonist which is generally used for the prophylactic management of nausea and vomiting; however, studies have found that ondansetron might decrease the incidence of PDPH. Therefore, we aimed to evalute the effect of ondansetron on decreasing the incidence of PDPH., METHODS: In this double-blind randomized placebo-controlled clinical trial, 210 parturients who underwent elective cesarean section under spinal anesthesia were randomly allocated to two groups. The intervention group received 0.15 mg/kg ondansetron, while the control group received 5 ml normal saline. Heart rate and mean arterial pressure (MAP) were recorded during surgery. Furthermore, postoperative nausea and vomiting (PONV) and PDPH in the two groups were noted by an anesthetic nurse for 3 days and compared., RESULTS: The incidence of PDPH in the intervention group was significantly lower than in the control group (P = 0.001). The incidence of PONV was also significantly lower in the intervention group compared to the control group (P < 0.05). However, MAP was significantly higher in the intervention group compared to the control group (P < 0.05). No significant difference was found between the two groups regarding heart rate (P > 0.05)., CONCLUSION: Ondansetron (0.15 mg/kg) appeared to reduce the incidence of PDPH, as well as the incidence of hypotension and PONV, in parturients undergoing spinal anesthesia for cesarean section.

Hahm TS, Hwang JW, Kim WH, et al. A prospective, randomized, double-blind, multicenter trial to evaluate the therapeutic efficacy and safety of palonosetron in the treatment of postoperative nausea and vomiting over a 72-h period. *J Anesth*. 2015;29(1):21-28.

PURPOSE: We performed a multicenter, randomized, double-blind trial to assess the efficacy and safety of a single, fixed, intravenous dose of palonosetron (0.075 mg) in the treatment of established postoperative nausea and vomiting (PONV)., METHODS: Three hundred and eighty-four patients who had at least one risk factors of PONV and underwent surgery under general anesthesia were screened. Those who developed PONV were randomized to receive either 0.075 mg intravenous palonosetron or a placebo. The incidence of nausea and vomiting, severity of

nausea, requirements for rescue anti-emetics, and adverse effects at 2, 24, and 72 h after drug administration were evaluated. Complete response (CR) and complete control (CC) rate were compared for 24 and 72 h., RESULTS: Among the 384 patients, 152 (39.6 %) developed PONV and were randomized to either the palonosetron (n = 75) or placebo (n = 77) group. The number of patients with CR at 24 and 72 h was higher in the palonosetron group than the placebo group [0-24 h: n = 49 (68.1 %) vs. n = 30 (40.5 %), p < 0.001; 0-72 h: n = 47 (65.3 %) vs. n = 28 (37.8 %), p < 0.001]. The incidence of PONV at 2, 24, and 72 h periods was lower in the palonosetron group than the placebo group (29.2, 45.8, and 50.0 % in the palonosetron group vs. 50.0, 62.2, and 66.2 % in the placebo group, p = 0.010, 0.048, 0.047, respectively). The incidence of adverse events was not different between the groups., CONCLUSION: A single 0.075 mg IV dose of palonosetron effectively increased the CR rates at 24 and 72 h in these moderate-risk patients with established PONV.

Hesketh PJ, Morrow G, Komorowski AW, Ahmed R, Cox D. Efficacy and safety of palonosetron as salvage treatment in the prevention of chemotherapy-induced nausea and vomiting in patients receiving low emetogenic chemotherapy (LEC). ***Support Care Cancer.*** **2012;20(10):2633-2637.**

PURPOSE: The purpose of this study is to evaluate the efficacy and safety of intravenous (IV) palonosetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients with cancer who had incomplete control of CINV during their previous cycle of low emetogenic chemotherapy (LEC). METHODS: Patients with histologically or cytologically confirmed cancer, >/=18 years of age, with a Karnofsky Performance Scale score of >/=50% who had received LEC that induced vomiting and/or at least moderate nausea during their previous treatment cycle received palonosetron 0.25 mg IV 30 min before chemotherapy. Outcomes were recorded in patient diaries over 120 h and at an end-of-study visit on days 6, 7, or 8 after LEC administration. The primary efficacy variable was the complete response rate, defined as no emetic episodes and no rescue medication at 0-24 h (acute post-chemotherapy phase), 24-120 h (delayed phase), and 0-120 h (overall). RESULTS: Complete responses among the intent-to-treat study population (n = 34) were recorded for 88.2 % of patients in the acute phase, 67.6% in the delayed phase, and 67.6% overall. No emetic episodes occurred in 91.2 and 79.4% of patients during the acute and delayed phases, respectively, and no nausea in 73.5 and 52.9%, respectively. Palonosetron was well tolerated; only two patients experienced treatment-related adverse events. CONCLUSIONS: Among the patients with cancer who had a history of CINV with LEC, palonosetron was effective in preventing CINV in both the acute and delayed post-chemotherapy phases, and was well tolerated. Randomized comparative studies in larger populations of patients receiving LEC are needed to confirm these findings.

Jung WS, Kim YB, Park HY, Choi WJ, Yang HS. Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy. ***J Anesth.*** **2013;27(3):396-401.**

PURPOSE: The use of opioids following surgery is associated with a high incidence of postoperative nausea and vomiting (PONV). We conducted a prospective, randomized, double-blind, placebo-controlled study to investigate the effect of orally administered aprepitant, a neurokinin-1 receptor antagonist, for reducing PONV in patients with fentanyl-based, patient-controlled analgesia (PCA) given intravenously after gynecological laparoscopy., METHODS: One hundred and twenty female patients (ages 21-60) undergoing laparoscopic hysterectomy were randomly allocated to receive 80 mg (A80 group, n = 40) or 125 mg aprepitant (A125 group, n = 40) or placebo (control group, n = 40) orally 2 h before anesthesia induction. Anesthesia was maintained with isoflurane and remifentanil, and PCA IV using fentanyl and ketorolac were provided for 48 h after surgery. Incidences of nausea, vomiting/retching, and use of rescue antiemetics were recorded at 2, 24, and 48 h after surgery. Complete response was defined as no PONV and no need for rescue treatment., RESULTS: The incidence of complete response was significantly lower in the A80 and A125 groups than in controls, 56 % and 63 %, vs. 28 %, respectively, P = 0.007 and P = 0.003, respectively, during the first 48 h, and 65 % and 65 % vs. 38 %, respectively, both P = 0.025, during the first 2 h. However, there were no statistically significant differences between A80 and A125 groups in the incidences of complete response and PONV during the study period., CONCLUSIONS: Aprepitant 80 mg orally was effective in lowering the incidence of PONV in the first 48 h after anesthesia in patients receiving fentanyl-based PCA after gynecological laparoscopy.

Kim S-H, Oh C-S, Lee SJ. Efficacy of palonosetron and ramosetron on postoperative nausea and vomiting related to intravenous patient-controlled analgesia with opioids after gynecological laparoscopic surgery (double-blinded prospective randomized controlled trial). *J Anesth.* 2015;29(4):585-592.

PURPOSE: The study was designed to assess the efficacy of palonosetron and ramosetron in preventing postoperative nausea and vomiting (PONV) related to intravenous (IV) patient-controlled analgesia (PCA) with opioids after gynecological laparoscopic surgery., METHODS: Patients were randomly allocated to 4 groups-C, P, R0.3 and RPCA. At the end of surgery, group C received an infusion of 50 ml normal saline, group P received palonosetron 75 mug mixed in 50 ml normal saline, and groups R0.3 and RPCA received ramosetron 0.3 mg mixed in 50 ml normal saline. A PCA pump containing fentanyl was connected for all groups; however, ramosetron 0.6 mg was mixed with the PCA regimen for the RPCA group. PONV and postoperative pain were assessed., RESULTS: PONV incidence and scale, and Rhodes index in RPCA group between 24 and 72 h after discharge from the post-anesthetic care unit (PACU) showed significantly lower values, compared with the other groups. PONV incidence and scale, and Rhodes index in P group and R0.3 group were lower than the corresponding values in C group at all times, without statistical significance., CONCLUSION: A single dose of palonosetron 75 mug or ramosetron 0.3 mg was unable to prevent PONV related to IV PCA with opioids in patients undergoing gynecological laparoscopic surgery. The combination of a single dose of

ramosetron 0.3 mg, followed by ramosetron 0.6 mg mixed with PCA, significantly decreased PONV compared with a single dose of palonosetron 75 mug or ramosetron 0.3 mg.

Koju RB, Gurung BS, Dongol Y. Prophylactic administration of ondansetron in prevention of intrathecal morphine-induced pruritus and post-operative nausea and vomiting in patients undergoing caesarean section. *BMC Anesthesiol.* 2015;15:18.

BACKGROUND: Intrathecal morphine is commonly used for post caesarean analgesia. However, their use is frequently associated with the incidence of troublesome side effects such as nausea, vomiting and pruritus. Various mechanisms have been postulated for the opioid-induced pruritus, with a variety of medications with different mechanisms of actions formulated for the prevention and treatment. But, the results are inconsistent and hence the prevention and treatment of opioid-induced pruritus still remains a challenge. Ondansetron which is antiemetic, non-sedative and has no antianalgesic effect is an antagonist to 5-HT3 receptor, the receptor with which opioids interacts and imparts its effects. Ondansetron, thus, would be an attractive treatment strategy for both opioid-induced pruritus and post-operative nausea and vomiting., METHODS: After the approval from institutional review committee and written consent received from the patient, 50 healthy parturients of ASA I and II physical status undergoing caesarean section under spinal anaesthesia were enrolled for the study. They were randomly categorized into placebo group (2 ml normal saline) and treatment group (2 ml of 4 mg ondansetron), each group containing 25 patients. Pruritus and post-operative nausea and vomiting scores were recorded up to 24 hours after the administration of intrathecal morphine. Statistical analysis was performed using chi-square test., RESULTS: The incidence, severity and necessity of treatment for pruritus in the treatment group was significantly reduced compared to the placebo group (16% vs 88%). Similarly, the risk of post-operative nausea and vomiting in the treatment group was less compared to the placebo group (8% vs 56%)., CONCLUSION: Prophylactic administration of ondansetron to parturients receiving intrathecal morphine for post-operative analgesia provides a significant reduction of intrathecal morphine-induced pruritus and nausea and vomiting., TRIAL REGISTRATION: CTRI/2015/01/005362 registered on 07/01/2015 in Clinical Trials Registry-India (ctri.nic.in).

Koren G, Clark S, Hankins GDV, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *Am J Obstet Gynecol.* 2010;203(6):571.e571-577.

OBJECTIVE: To evaluate the effectiveness of Diclectin (doxylamine succinate 10 mg-pyridoxine hydrochloride 10 mg, delayed-release preparation) as compared with placebo for nausea and vomiting of pregnancy., STUDY DESIGN: A randomized, double-blind, multicenter placebo controlled trial studying pregnant women suffering from nausea and vomiting of pregnancy, analyzed by intention to treat. Women received Diclectin (n = 131) or placebo (n = 125) for 14 days. Nausea and vomiting of pregnancy symptoms were evaluated daily using the pregnancy unique quantification of emesis scale., RESULTS: Diclectin use resulted in a significantly larger

improvement in symptoms of nausea and vomiting of pregnancy compared with placebo based on both the pregnancy unique quantification of emesis score (-4.8 +/- 2.7 vs -3.9 +/- 2.6; P = .006) and quality of life. After the trial, 64 (48.9%) women receiving Diclectin asked to continue compassionate use of their medication, as compared with 41 (32.8%) of placebo-treated women (P = .009)., CONCLUSION: Diclectin delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating nausea and vomiting of pregnancy.

Koren G, Clark S, Hankins GDV, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. *BMC Pregnancy Childbirth*. 2015;15:59.

(See also Koren 2010)

BACKGROUND: Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy, affecting up to 80% of expecting mothers. In April 2013 the FDA approved the delayed release combination of doxylamine succinate and -pyridoxine hydrochloride (Diclegis) for NVP, following a phase 3 randomized trial in pregnant women. The fetal safety of this medication has been proven by numerous studies. However, because it is the only FDA-approved medication for NVP that is likely to be used by a large number of pregnant women, its maternal safety is an important public health question. The Objective is to evaluate the maternal safety of doxylamine succinate -pyridoxine hydrochloride delayed-release preparation (Diclegis as compared to placebo., METHODS: We randomized women suffering from NVP to receive Diclegis (n=131) or placebo (n=125) for 14 days at doses ranging from 2-4 tablets a day, based on a pre-specified titration protocol response to symptoms. Adverse events were collected through patient diaries, clinical examination and laboratory testing., RESULTS: Doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg use was not associated with an increased rate of any adverse event over placebo, including CNS depression, gastrointestinal or cardiovascular involvement., CONCLUSIONS: Doxylamine succinate-pyridoxine hydrochloride delayed release combination is safe and well tolerated by pregnant women when used in the recommended dose of up to 4 tablets daily in treating nausea and vomiting of pregnancy., TRIAL REGISTRATION: Clinical Trial Registration No: NCT00614445 .

Lim CS, Ko YK, Kim YH, et al. Efficacy of the oral neurokinin-1 receptor antagonist aprepitant administered with ondansetron for the prevention of postoperative nausea and vomiting. *Korean J Anesthesiol*. 2013;64(3):212-217.

BACKGROUND: 5-HT3 receptor antagonist, dexamethasone and droperidol were used for the prevention of postoperative nausea and vomiting (PONV). Recently, neurokinin-1 (NK1) antagonist has been used for PONV. We evaluated the effect of oral aprepitant premedication in addition to ondansetron. METHODS: A total 90 patients scheduled for elective rhinolaryngological surgery were allocated to three groups (Control, Ap80, Ap125), each of 30 at

random. Ondansetron 4 mg was injected intravenously to all patients just before the end of surgery. On the morning of surgery, 80 mg and 125 mg aprepitant were additionally administered into the Ap80 group and Ap125 group, respectively. The rhodes index of nausea, vomiting and retching (RINVR) was checked at 6 hr and 24 hr after surgery. RESULTS: Twelve patients who used steroids unexpectedly were excluded. Finally 78 patients (control : Ap80 : Ap125 = 24 : 28 : 26) were enrolled. Overall PONV occurrence rate of Ap125 group (1/26, 3.9%) was lower (P = 0.015) than the control group (7/24, 29.2%) at 6 hr after surgery. The nausea distress score of Ap125 group (0.04 +/- 0.20) was lower (P = 0.032) than the control group (0.67 +/- 1.24) at 6 hr after surgery. No evident side effect of aprepitant was observed. CONCLUSIONS: Oral aprepitant 125 mg can be used as combination therapy for the prevention of PONV.

Maehara M, Ueda T, Miyahara D, et al. Clinical efficacy of aprepitant in patients with gynecological cancer after chemotherapy using paclitaxel and carboplatin. *Anti-cancer Res.* 2015;35(8):4527-4534.

AIM: This study aimed to evaluate the efficacy of aprepitant, a neurokinin (NK)1 receptor antagonist, on chemotherapy-induced nausea and vomiting (CINV)., PATIENTS AND METHODS: A randomized, open-labeled, parallel-design study was undertaken in gynecologic-cancer (GC) patients at the Fukuoka University Hospital. Twenty-three patients were divided into without (group A) or with aprepitant (Group B) in the first cycle of paclitaxel and carboplatin (TC) therapy. From the second cycle onwards, all patients used aprepitant. Statistical significance was assessed using McNemar and Chi-square tests., RESULTS: In the first cycle, the prevalence of a complete response, no episodes of nausea or food intake in group B was significantly increased compared to group A. No significant difference in the prevalence of a complete response or food intake situation was found from the second cycle onwards., CONCLUSION: Combination of aprepitant with standard anti-emetic therapy may contribute to prevention of CINV in TC therapy for GC patients.

Reeve BK, Cook DJ, Babineau D, Scholes LC, Buckley DN. Prophylactic Diclectin reduces the incidence of postoperative vomiting. *Can J Anesth.* 2005;52(1):55-61.

BACKGROUND: Diclectin(R) (DCL) is an effective antiemetic used for relief of nausea and vomiting in pregnancy. It is unknown whether DCL is effective in the prevention of postoperative nausea and vomiting (PONV)., METHODS: We conducted a randomized, stratified, double-blind placebo-controlled trial to examine the incidence of PONV in women undergoing elective laparoscopic tubal ligation in the day surgery setting. DCL (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) was administered orally the night before surgery, the morning of surgery, and upon hospital discharge., RESULTS: We enrolled 146 women in the trial, 127 of whom were included in the effectiveness analysis and 102 of whom were included in the efficacy analysis. We did not detect a difference in the incidence of nausea and vomiting in the first six

hours postoperatively after adjusting for additional antiemetics administered. Patients receiving DCL as compared with placebo were significantly less likely to experience vomiting six to 24 hr postoperatively [5/59 (8.5%) vs 14/55 (25.4%), P < 0.017]. Treated patients tended to return to work earlier than those who received placebo (1.74 vs 3.7 days P = NS)., CONCLUSION: Perioperative oral DCL reduces the incidence of postoperative vomiting in women undergoing elective laparoscopic tubal ligation, and may accelerate return to work.

Saito H, Yoshizawa H, Yoshimori K, et al. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. *Ann Oncol.* 2013;24(4):1067-1073.

BACKGROUND: We evaluated the efficacy and safety of single-dose fosaprepitant in combination with intravenous granisetron and dexamethasone., PATIENTS AND METHODS: Patients receiving chemotherapy including cisplatin (>=70 mg/m(2)) were eligible. A total of 347 patients (21% had received cisplatin with vomiting) were enrolled in this trial to receive the fosaprepitant regimen (fosaprepitant 150 mg, intravenous, on day 1 in combination with granisetron, 40 mug/kg, intravenous, on day 1 and dexamethasone, intravenous, on days 1-3) or the control regimen (placebo plus intravenous granisetron and dexamethasone). The primary end point was the percentage of patients who had a complete response (no emesis and no rescue therapy) over the entire treatment course (0-120 h)., RESULTS: The percentage of patients with a complete response was significantly higher in the fosaprepitant group than in the control group (64% versus 47%, P = 0.0015). The fosaprepitant regimen was more effective than the control regimen in both the acute (0-24 h postchemotherapy) phase (94% versus 81%, P = 0.0006) and the delayed (24-120 h postchemotherapy) phase (65% versus 49%, P = 0.0025)., CONCLUSIONS: Single-dose fosaprepitant used in combination with granisetron and dexamethasone was well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Tanioka M, Kitao A, Matsumoto K, et al. A randomised, placebo-controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy. *Brit J Cancer.* 2013;109(4):859-865.

BACKGROUND: We evaluated the efficacy of aprepitant plus granisetron and an increased dose of dexamethasone in selected patients undergoing moderately emetogenic chemotherapy (MEC)., METHODS: Nondrinking women <70 years undergoing MEC were randomly assigned to aprepitant (day 1, 125 mg; days 2 and 3, 80 mg) or placebo. Dexamethasone on days 1-3 was 12, 4, and 4 mg with aprepitant and 20, 8, and 8 mg with placebo. The primary end point was complete response (CR; no emesis or rescue therapy) during 120 h of the first cycle. Logistic regression analysis was performed to identify predictors of overall CR., RESULTS: Of the 94 patients enrolled, 91 were assessable. Most received carboplatin-based chemotherapy. In the

aprepitant (n=45) and placebo (n=46) groups, the overall, acute (day 1), and delayed (days 2-5) CR rates were 62% and 52%, 98% and 96%, and 62% and 52%, respectively. Although not statistically significant, the overall CR rate was 10% higher in the aprepitant group. Both regimens were well tolerated. On multivariate analysis, advanced ovarian cancer (OR, 0.26 (0.10-0.72)) was independently associated with a lower CR., CONCLUSION: Even with an increased dose of dexamethasone, aprepitant seemed more effective than placebo in these selected patients undergoing MEC; however, delayed phase management remains a significant problem.

Terkawi AS, Tiouririne M, Mehta SH, Hackworth JM, Tsang S, Durieux ME. Ondansetron does not attenuate hemodynamic changes in patients undergoing elective cesarean delivery using subarachnoid anesthesia: a double-blind, placebo-controlled, randomized trial. *Region Anesth Pain M.* 2015;40(4):344-348.

INTRODUCTION: Hypotension is the most common complication after subarachnoid anesthesia for cesarean delivery. Several therapeutic and preventive measures are used to attenuate this side effect. Serotonin receptor-blocking drugs have been suggested as one such approach. We sought to determine whether prophylactically administered intravenous ondansetron could attenuate hypotension in patients undergoing elective cesarean delivery performed under subarachnoid anesthesia., METHODS: Eighty-six patients undergoing elective cesarean delivery were recruited and randomly allocated to receive either 8 mg intravenous ondansetron (group O; n = 44) or placebo (group P; n = 42) in a prospective double-blind design. Systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP), and heart rate (HR) were measured at baseline and at 3-minute intervals from the time of initiation of subarachnoid anesthesia until delivery. Ondansetron effect on hemodynamics (SBP, DBP, MAP, and HR) was quantified and analyzed using a linear mixed effect model., RESULTS: We did not find differences in SBP (P = 0.78), MAP (P = 0.89), DBP (P = 0.82), or HR (P = 0.18) between the 2 groups during the study period. Phenylephrine requirements to treat hypotension were 350 mug (175-700 mug) in group O and 450 mug (300-700 mug) in group P (P = 0.30). The incidence of pruritus was 63% (n = 28 of 44) in group O and 56% (n = 23 of 42) in group P (difference, 0.08 [95% confidence interval, -0.23 to 0.41], P = 0.59). No difference in the incidence of nausea and vomiting or sensory level was found., CONCLUSIONS: Ondansetron premedication does not attenuate hemodynamic changes after subarachnoid anesthesia nor does it reduce the amount of vasopressor use, pruritus, or nausea and vomiting.

Vallejo MC, Phelps AL, Ibinson JW, et al. Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery. *Plast Reconstr Surg.* 2012;129(2):519-526.

BACKGROUND: Postoperative nausea and vomiting is a major challenge in the perioperative setting. The incidence can be as high as 80 percent, and the majority of the symptoms among outpatients occur after discharge. This study evaluated the efficacy of a neurokinin-1 receptor antagonist (aprepitant) in reducing postoperative symptoms for up to 48 hours in patients

undergoing outpatient plastic surgery., METHODS: A prospective, double-blinded, randomized, two-arm evaluation of 150 ambulatory plastic surgery patients receiving a standardized general anesthetic, including postoperative nausea and vomiting prophylaxis with ondansetron and either aprepitant or placebo, was performed. The main outcome measures were the occurrence of vomiting and the severity of nausea for up to 48 hours postoperatively., RESULTS: Overall, 9.3 percent of patients who received aprepitant versus 29.7 percent in group B had vomiting, with the majority of vomiting episodes occurring after hospital discharge. The Kaplan-Meier plot of the hazards of vomiting revealed an increased incidence of emesis in patients receiving ondansetron alone compared with the combination of ondansetron and aprepitant (p = 0.006). The incidence of nausea was not significantly different in the two groups. Severity of nausea, however, was significantly higher in those receiving ondansetron alone compared with those receiving ondansetron and aprepitant, as measured by a peak nausea score (p = 0.014) and by multivariate analysis of variance results comparing repeated verbal rating scale scores over 48 hours after surgery (p = 0.024)., CONCLUSION: In patients undergoing plastic surgery, the addition of aprepitant to ondansetron significantly decreases postoperative vomiting rates and nausea severity for up to 48 hours postoperatively., CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Wagner DS, Gauger V, Chiravuri D, Faust K. Ondansetron oral disintegrating tablets for the prevention of postoperative vomiting in children undergoing strabismus surgery. *Ther Clin Risk Manag.* 2007;3(4):691-694.

Strabismus surgery in pediatric patients is associated with a high incidence of postoperative nausea and vomiting (PONV). Ondansetron disintegrating tablets (ODT), an oral freeze-dried formulation of the 5-HT(3) antagonist, are well-tolerated and have been shown to reduce chemotherapy-induced vomiting. The purpose of this study was to assess the efficacy of the ODT in preventing postoperative vomiting (POV) in children undergoing strabismus repair. Healthy children aged 4-12 years of age were administered a 4 mg ODT 30 minutes prior to the induction of general anesthesia. Induction and maintenance of anesthesia were standardized; each child received acetaminophen and ketorolac pre-emptively for analgesia. This study group was compared with a historical control group who received a placebo in previously conducted identical trials of POV. The 35 children included in this study were compared with 31 controls. The incidence and severity of POV and use of rescue antiemetics were significantly lower in children who received ODT compared with placebo (p </= 0.001). The acute complete response (ie, no emesis and no rescue antiemetics in 24 hours) was 76% in the ODT group compared with 16% in the controls (p </= 0.001). Results suggest that ODT given preoperatively reduces the incidence and severity of POV in children undergoing strabismus surgery.

Zhang D, Shen Z, You J, Zhu X, Tang Q-F. Effect of ondansetron in preventing postoperative nausea and vomiting under different conditions of general anesthesia: a preliminary, randomized, controlled study. *Ups J Med Sci.* 2013;118(2):87-90.

METHODS: Two hundred and forty patients were randomly allocated into six groups: Group I, anesthesia was maintained with sevoflurane; Group II, anesthesia was maintained with sevoflurane and 8 mg of ondansetron; Group III, anesthesia was maintained with propofol; Group IV, anesthesia was maintained with propofol and 8 mg of ondansetron; Group V, anesthesia was maintained with sevoflurane and propofol; Group VI, anesthesia was maintained with sevoflurane combined with propofol and 8 mg of ondansetron., RESULTS: We found that the incidence of vomiting was lower in group II (17.5%), group IV (7.5%), and group VI (10%) compared with group I (55%), group III (27.5%), and group V (30%), respectively ($P < 0.05$). The incidence of vomiting was also lower in group III (27.5%) and group V (30%) when compared with group I (55%) ($P < 0.05$). The incidence of nausea was 55% in group I, 42.5% in group II, 30% in group III, 27.5% in group IV, 30% in group V, and 30% in group VI. Groups III and V had a lower incidence of nausea than group I ($P < 0.05$)., CONCLUSIONS: We conclude that compared with sevoflurane anesthesia alone, anesthesia with either propofol alone or propofol combined with sevoflurane resulted in a reduced incidence of vomiting and nausea during the first 24 h after surgery. Administration of ondansetron effectively reduced the incidence of vomiting but not that of nausea for all three types of general anesthesia.