

Drug Class Review on Newer Antiemetics



Preliminary Update Scan Report #2

December 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Original Final Report January 2006 (searches through February 2005)

Date of Last Update Scan:

November 2006

SCOPE AND KEY QUESTIONS:

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Question 1: What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting?

Key Question 2: What is the comparative tolerability and safety of Newer Antiemetics when used to treat or prevent nausea and/or vomiting?

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), pregnancy, other medications, or co-morbidities for which one Newer Antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria**Population(s):**

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

- Chemotherapy*

- Radiation Therapy
- Post-Operative
- Pregnancy

* In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999(Hesketh, Kris et al. 1997; Hesketh 1999) to clarify the level of emetogenicity of the chemotherapeutic regimen with which the cancer population of the study is being treated. This scale rates the emetogenic potential of the chemotherapeutic agent (or combination of agents) given to a cancer patient as if the patient would not be receiving any antiemetic drugs – i.e., it classifies the chemotherapeutic agents according to the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as “1” on this scale have a low emetogenic potential, while agents rated as “5” are considered to be severely emetogenic (a >90% chance of emesis in patients).

Interventions

Table 1. Antiemetic Drug Indications and Recommended Doses

Generic Name	Trade Name	FDA Approved Indications and Dosage in Adults	FDA Approved Indications and Dosage in Children
Aprepitant	Emend®	Chemotherapy: Day 1: 125 mg po once Days 2 & 3: 80 mg po once <i>Emend is to be given for 3 days in conjunction with a regimen containing a 5HT3-antagonist and a corticosteroid</i>	Chemotherapy: Dose determined by doctor
Dolasetron	Anzemet®	Chemotherapy: 100 mg po once (up to 1 hr before chemo) 1.8 mg/kg iv once (up to 30 min before chemo); Alternatively, a fixed dose of 100mg iv can be administered over 30sec. PONV, prevention: 100 mg po once (up to 2 hrs before surgery) 12.5 mg iv once (15 min. before anesthesia ends) PONV, established: 12.5 mg iv once (at onset of symptoms)	Chemotherapy (for children 2-16years): 1.8 mg/kg po & iv once, max. 100mg (up to 30 min before chemo) PONV, prevention: 0.35 mg/kg iv once , max. 12.5 mg (15 min before anesthesia ends) 1.2 mg/kg po once , max. 100mg (up to 2 hrs before surgery) PONV, established: 0.35 mg/kg iv once, max. 12.5mg (at onset of symptoms)
Granisetron	Kytril®	Chemotherapy: 2 mg po once (up to 1 hr before chemo) 0.10mg/kg iv once (up to 30 min before chemo) PONV, prevention: 1 mg iv once (before induction or before reversal of anesthesia) PONV, established: 1 mg iv once Radiation: 2 mg po once	Chemotherapy: 0.10 mg/kg iv once (up to 30 min before chemo)

Ondansetron	Zofran®	<p>Chemotherapy: <i>Moderately emetogenic:</i> 8 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given twice daily <i>Highly emetogenic:</i> single 24 mg tablet 30 min before chemo; 32 mg iv once (30 min before chemo) or 0.15 mg/kg tid (1st dose is infused 30 min before chemo starts) PONV, prevention: 4 mg iv once (immediately before induction of anesthesia) 16 mg po (tablet or orally disintegrating tablet) once (1 hr before anesthesia induction) (20 mL if oral solution given) PONV, established: 4 mg iv or im once (at onset of symptoms) Radiation: 8 mg po (tablet or orally disintegrating tablet) X3 (10 mL X3 if oral solution given) (1st dose 1-2 hours before radiation)</p>	<p>Chemotherapy <i>Moderately emetogenic:</i> for patients aged 12 years and above, the dosage is the same as in adults; for patients 4-11 years the dose is 4 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given three times daily 0.15mg/kg iv once (30 min before chemo) PONV, prevention (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV): 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg PONV, established (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV): 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg</p>
Palonosetron	Aloxi®	<p>Chemotherapy: 0.25 mg iv once (up to 30 minutes before chemo)</p>	<p>Chemotherapy: Dose determined by doctor</p>

po = (*per os*) orally
 iv = intravenous
 im = intramuscular

Effectiveness outcomes

Treatment of Established Post-Operative Nausea and/or Vomiting

- Success: absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient.
 - Early: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - Early: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of Post-Operative Nausea and/or Vomiting

- Success: absence of vomiting and/or retching in the post-operative period.
 - Acute: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the post-operative period.
 - Acute: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively

- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of Nausea and/or Vomiting related to Chemotherapy

- Success: absence of vomiting and/or retching
 - during the first 24 hours of chemotherapy administration
 - acute/early vomiting and/or retching induced by highly emetogenic chemotherapy
 - acute/early vomiting and/or retching induced by moderately emetogenic chemotherapy
 - after the first 24 hours of chemotherapy administration
 - delayed/late vomiting and/or retching induced by highly emetogenic chemotherapy
 - delayed/late vomiting and/or retching induced by moderately emetogenic chemotherapy
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - during the first 24 hours of chemotherapy administration
 - acute: induced by highly emetogenic chemotherapy
 - acute: induced by moderately emetogenic chemotherapy
 - after the first 24 hours of chemotherapy administration
 - delayed: induced by highly emetogenic chemotherapy
 - delayed: induced by moderately emetogenic chemotherapy
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, worst day nausea/ vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention Radiation Induced Nausea and/or Vomiting

- Success: absence of vomiting and/or retching
 - Acute: during the first 24 hours of onset of radiotherapy
 - Delayed: after the first 24 hours of onset of radiotherapy, or after consecutive radiotherapy doses given during several days
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - Acute: during the first 24 hours of onset of radiotherapy
 - Delayed: after the first 24 hours of onset of radiotherapy, or after consecutive radiotherapy doses given during several days
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, worst day nausea/ vomiting and/or retching, delay until first emetic episode, number of emesis-free days

**Treatment of Nausea and/or Vomiting Associated with Pregnancy
(including Hyperemesis Gravidarum)**

- Success: absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman.
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
- Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes per period of time, number of or need for rescue medication, serious emetic sequelae, number of emesis-free days, re-hospitalization episodes and/or duration.

Wherever possible, data on effective dose range, dose-response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (headache, constipation, dizziness, sedation, etc.)

Study designs

1. For effectiveness, controlled clinical trials and good-quality systematic reviews.
2. For safety, in addition to controlled clinical trials, observational studies will be included.

METHODS**Literature Search**

To identify relevant citations, we searched MEDLINE (October 2006 through November 2007). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 64 citations. Of those, there are 10 new potentially relevant controlled clinical trials (Appendix A). Taken together with the 19 new potentially relevant controlled clinical trials identified in Preliminary Update Scan #1 (November 2006), now there are a total of 29.

The majority of the 10 new trials involve head-to-head comparisons of two included drugs. The table below provides a summary of how this new evidence may address some of the gaps in the previous report.

Trial	Population	Comparison	Special Consideration
Aapro 2006	<i>Highly</i> emetogenic Chemotherapy - adults	Palonosetron vs ondansetron	2 previous HTH trials involving palonosetron in patients undergoing <i>moderately</i> emetogenic chemo
Abali 2007	Chemotherapy – adults	Granisetron vs ondansetron	Turkish patients
Birmingham 2006	PONV – adults	Dolasetron vs ondansetron	Already have 5 HTH trials of this comparison
Candiotti 2007	Breakthrough PONV – adults	Granisetron vs ondansetron	Falls in between prophylaxis and treatment of established – no previous trials with this focus
Diemunsch 2007	PONV – adults	Aprepitant vs ondansetron	First HTH trial involving aprepitant <i>monotherapy</i> ; previously only trials involving aprepitant were as add-on
Gan 2007	PONV – adults	Aprepitant vs ondansetron	Another HTH trial involving aprepitant <i>monotherapy</i> ; previously only trials involving aprepitant were as add-on
Hesketh 2006	Chemotherapy – adults	Pooled analysis from 2 previously included trials of add-on aprepitant	KQ3 – looking at effects of gender
Luisi 2006	Chemotherapy – children	Granisetron vs metoclopramide	Few HTH trials, using placebo- controlled and active- controlled trials to address gap
Schmoll 2006	Chemotherapy – adults	Add-on aprepitant vs placebo	Similar to previously included trials
Subramaniam 2007	PONV – children	Ondansetron vs placebo	Few HTH trials, using placebo- controlled and active- controlled trials to address gap

Other gaps potentially addressed by evidence from the previous preliminary update scan #1 included:

- (1) Ondansetron orally disintegrating tablets: 2 new trials comparing the ODT to the IV form of ondansetron were the first trials to directly compare the ODT to any other newer antiemetic.
- (2) Treatment of *established* nausea/vomiting: HTH trial of IV dolasetron vs IV ondansetron was first HTH for this population
- (3) Dolasetron vs granisetron for PONV prevention in adults: New HTH trial of dolasetron vs granisetron was first HTH trial for this comparison in this population. Previously, our comparison of dolasetron vs granisetron was based on indirect evidence only.

New Drugs

None

New Indications

None

New Safety Alerts

Dolasetron

Modification			
Source	Date	Type	Details
FDA	5/07	Label change: Precautions	Added: Dolasetron should be administered with caution in pediatric patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. Rare cases of sustained supraventricular and ventricular arrhythmias, cardiac arrest leading to death, and myocardial infarction have been reported in children and adolescents
FDA	9/07	Label change: Adverse reactions	Added postmarketing experience information: There are rare reports of wide complex tachycardia or ventricular tachycardia and of ventricular fibrillation cardiac arrest following intravenous administration.

APPENDIX A

Aapro, M. S., S. M. Grunberg, et al. (2006). "A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy." Annals of Oncology 17(9): 1441-9.

BACKGROUND: This pivotal phase III trial evaluated the efficacy and safety of palonosetron in preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV) following highly emetogenic chemotherapy (HEC). **PATIENTS AND METHODS:** Patients were randomized to a single intravenous dose of palonosetron 0.25 mg or 0.75 mg, or ondansetron 32 mg prior to HEC. Dexamethasone pre-treatment (with stratification) was used at investigator discretion. The primary efficacy endpoint was the proportion of patients with complete response (CR) during the first 24 h post-chemotherapy (acute phase). **RESULTS:** In the intent-to-treat analysis (n = 667), palonosetron 0.25 mg and 0.75 mg were at least as effective as ondansetron in preventing acute CINV (59.2%, 65.5%, and 57.0% CR rates, respectively); CR rates were slightly higher with palonosetron than ondansetron during the delayed (24-120 h) and overall (0-120 h) phases. Two thirds of patients (n = 447) received concomitant dexamethasone. Patients pre-treated with palonosetron 0.25 mg plus dexamethasone had significantly higher CR rates than those receiving ondansetron plus dexamethasone during the delayed (42.0% versus 28.6%) and overall (40.7% versus 25.2%) phases. Palonosetron and ondansetron were well tolerated. **CONCLUSIONS:** Single-dose palonosetron was as effective as ondansetron in preventing acute CINV following HEC, and with dexamethasone pre-treatment, its effectiveness was significantly increased over ondansetron throughout the 5-day post-chemotherapy period.

Abali, H. and I. Celik (2007). "Tropisetron, ondansetron, and granisetron for control of chemotherapy-induced emesis in Turkish cancer patients: a comparison of efficacy, side-effect profile, and cost." Cancer Investigation 25(3): 135-9.

BACKGROUND: Tropisetron, ondansetron, and granisetron are considered equally efficacious, supported by several international studies. However, there are interindividual variations in their metabolism that could affect efficacy. The clustering of such variations may change from one to another nation. Therefore, their equality must be validated in Turkish patients. The aim of this study was to compare their efficacies, side-effect profiles, and costs in the prophylaxis of emesis induced by moderate to high emetogenic chemotherapies. **METHODS:** A total of 158 patients with a median age of 48 years, 115 (72.8 percent) female and 43 (27.2 percent) male, were included, respectively. Fifty-one, 61, and 46 patients were allocated to tropisetron (5 mg), ondansetron (8 mg), and granisetron (3 mg IV) in combination with 8 mg dexamethasone, which were continued 5 mg once a day, 8 mg b.i.d. and 1 mg b.i.d. PO for 5 days, respectively. **RESULTS:** The complete response (CR) rates in the control of acute emesis were 80.4 percent with tropisetron, 72.1 percent with ondansetron, and 71.7 percent granisetron (p = 0.877). CR rates in delayed emesis (Days 2-5) were 68.6 percent, 68.9 percent, and 76.1 percent, respectively (p = 0.527). Rates of freedom from nausea in the same period were 37.3 percent, 35.9 percent, and 33.9 percent (p = 0.949). Nausea control rates, side-effect profile did not differ. However, headache seemed to be encountered higher (45.6 percent) in Turkish patients than others (3.9-9 percent). Tropisetron is the least expensive one (\$95.3 per cycle) according to current prices in Turkey. **CONCLUSIONS:** There were no differences among the 3 serotonin antagonists with respect to efficacy and frequency of side-effects in our patients. Tropisetron is the least expensive at current prices. The choice may be based on other parameters, such as ease of administration and patient preference.

Birmingham, S. D., B. W. Mecklenburg, et al. (2006). "Dolasetron versus ondansetron as single-agent prophylaxis for patients at increased risk for postoperative nausea and vomiting: a prospective, double-blind, randomized trial." Military Medicine 171(9): 913-6.

This study identified 100 ambulatory surgery patients receiving general anesthesia who were at increased risk for postoperative nausea and vomiting (PONV) and randomly assigned them to receive single-agent prophylaxis (12.5 mg of dolasetron or 4 mg of ondansetron) 15 to 30 minutes before the end of surgery. Data were collected in the postanesthesia care unit, and patients completed a questionnaire 24 hours after surgery. No statistically significant difference existed between study groups in demographic features, history of PONV, history of motion sickness, or type and duration of surgery and anesthesia. No statistically significant difference existed in satisfaction with the medication used for PONV prophylaxis (dolasetron, 70.9 of 100 mm; ondansetron, 67.9 of 100 mm; $p = 0.69$). No statistically significant difference existed in satisfaction with the overall surgical experience (dolasetron, 87.9 of 100 mm; ondansetron, 85.3 of 100 mm; $p = 0.36$). Costminimization strategies should be considered without fear of substandard care or increased patient dissatisfaction.

Candiotti, K. A., F. Nhuch, et al. (2007). "Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study." Anesthesia & Analgesia 104(6): 1370-3.

INTRODUCTION: Patients with an increased risk of postoperative nausea and vomiting (PONV) are frequently given prophylactic doses of a selective 5-hydroxytryptamine-3 antagonist (5HT₃). In chemotherapy patients, it has been demonstrated that after unsuccessful treatment with one 5HT₃ administering a different 5HT₃ alleviated symptoms. We hypothesized that we could define a benefit of a 5HT₃, cross-over in a pilot study of PONV. Two-hundred-fifty female patients received prophylactic ondansetron 4 mg at the end of a surgical procedure requiring general anesthesia and were then followed postoperatively for 4 h. **METHODS:** Eighty-eight women developed PONV and were randomly assigned to receive a repeat dose of ondansetron 4 mg ($n = 30$), granisetron 1 mg ($n = 30$), or granisetron 0.1 mg ($n = 28$) and then followed for 24 h. **RESULTS:** Patients receiving the repeat dose of ondansetron showed a complete response of 57%. Those receiving 1 or 0.1 mg doses of granisetron had rates of 60% and 68%, respectively. This difference was not statistically significant ($P = 0.773$). **CONCLUSION:** Unlike patients with chemotherapy-induced nausea and vomiting, perioperative patients who failed ondansetron prophylaxis did not have a significant response to cross-over dosing with granisetron.

Diemunsch, P., T. J. Gan, et al. (2007). "Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery." British Journal of Anaesthesia 99(2): 202-11.

BACKGROUND: The neurokinin(1) antagonist aprepitant is effective for prevention of chemotherapy-induced nausea and vomiting. We compared aprepitant with ondansetron for prevention of postoperative nausea and vomiting. **METHODS:** Nine hundred and twenty-two patients receiving general anaesthesia for major abdominal surgery were assigned to receive a single preoperative dose of oral aprepitant 40 mg, oral aprepitant 125 mg, or i.v. ondansetron 4 mg in a randomized, double-blind trial. Vomiting episodes, use of rescue therapy, and nausea severity (verbal rating scale) were documented for 48 h after surgery. Primary efficacy endpoints were complete response (no vomiting and no use of rescue therapy) 0-24 h after surgery and no vomiting 0-24 h after surgery. The secondary endpoint was no vomiting 0-48 h after surgery. **RESULTS:** Aprepitant at both doses was non-inferior to ondansetron for complete response 0-24 h after surgery (64% for aprepitant 40 mg, 63% for aprepitant 125 mg, and 55% for ondansetron, lower bound of 1-sided 95% CI > 0.65), superior to ondansetron for no vomiting 0-24 h after surgery (84% for aprepitant 40 mg, 86% for aprepitant 125 mg, and 71% for ondansetron; $P < 0.001$), and superior for no vomiting 0-48 h after surgery (82% for aprepitant, 40 mg, 85% for aprepitant, 125 mg, and 66% for ondansetron; $P < 0.001$). The distribution of peak nausea scores was lower in both aprepitant groups vs ondansetron ($P < 0.05$). **CONCLUSIONS:** Aprepitant was non-inferior to ondansetron in achieving complete response for 24 h after surgery. Aprepitant was

significantly more effective than ondansetron for preventing vomiting at 24 and 48 h after surgery, and in reducing nausea severity in the first 48 h after surgery. Aprepitant was generally well tolerated.

Gan, T. J., C. C. Apfel, et al. (2007). "A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting." Anesthesia & Analgesia 104(5): 1082-9.

BACKGROUND: Antiemetics currently in use are not totally effective. Neurokinin-1 receptor antagonists are a new class of antiemetic that have shown promise for chemotherapy-induced nausea and vomiting. This is the first study evaluating the efficacy and tolerability of the neurokinin-1 receptor antagonist, aprepitant, for the prevention of postoperative nausea and vomiting. **METHODS:** In this multicenter, double-blind trial, we randomly assigned 805 patients receiving general anesthesia for open abdominal surgery to a preoperative dose of aprepitant 40 mg orally, aprepitant 125 mg orally, or ondansetron 4 mg IV. Vomiting, nausea, and use of rescue therapy were assessed over 48 h after surgery. Treatments were compared using logistic regression. **RESULTS:** Incidence rates for the primary end point (complete response [no vomiting and no use of rescue] over 0-24 h after surgery, tested for superiority of aprepitant) were not different across groups (45% with aprepitant 40 mg, 43% with aprepitant 125 mg, and 42% with ondansetron). The incidence of no vomiting (0-24 h) was higher with aprepitant 40 mg (90%) and aprepitant 125 mg (95%) versus ondansetron (74%) ($P < 0.001$ for both comparisons), although between-treatment use of rescue and nausea control was not different. Both aprepitant doses also had higher incidences of no vomiting over 0-48 h ($P < 0.001$). No statistically significant differences were seen among the side effect profiles of the treatments. **CONCLUSIONS:** Aprepitant was superior to ondansetron for prevention of vomiting in the first 24 and 48 h, but no significant differences were observed between aprepitant and ondansetron for nausea control, use of rescue, or complete response.

Hesketh, P. J. (1999). "Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice." Oncologist 4(3): 191-196.

Hesketh, P. J., S. M. Grunberg, et al. (2006). "Combined data from two phase III trials of the NK1 antagonist aprepitant plus a 5HT₃ antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response." Supportive Care in Cancer 14(4): 354-60.

GOALS OF WORK: Prevention of chemotherapy-induced nausea and vomiting (CINV) with standard antiemetics has been more difficult to achieve in female patients. Data from two phase III trials of the NK1 antagonist aprepitant were assessed for potential effect of gender on treatment response. **PATIENTS AND METHODS:** 1,044 patients receiving cisplatin ($> \text{or} = 70 \text{ mg/m}^2$) were randomly assigned to control regimen [ondansetron (O) 32 mg i.v. and dexamethasone (D) 20 mg p.o. on day 1; D 8 mg twice daily on days 2-4] or aprepitant (A) regimen (A 125 mg p.o. plus O 32 mg and D 12 mg on day 1; A 80 mg and D 8 mg once daily on days 2-3; and D 8 mg on day 4). The primary endpoint was overall complete response (no emesis and no rescue therapy over days 1-5). Data were analyzed by a modified intent-to-treat approach. Between-treatment comparisons for each gender were made using logistic regression. **MAIN RESULTS:** Women comprised 42 and 43% of the aprepitant and control groups, respectively. In the control group, 41% of women had overall complete response compared with 53% of men. In the aprepitant group, 66% of women had overall complete response compared with 69% of men. **CONCLUSION:** The addition of aprepitant may negate the adverse prognostic effect of female gender on the prevention of CINV in patients receiving highly emetogenic chemotherapy.

Hesketh, P. J., M. G. Kris, et al. (1997). "Proposal for classifying the acute emetogenicity of cancer chemotherapy." Journal of Clinical Oncology 15(1): 103-9.

Luisi, F. A. V., A. S. Petrilli, et al. (2006). "Contribution to the treatment of nausea and emesis induced by chemotherapy in children and adolescents with osteosarcoma." Sao Paulo Medical Journal = Revista Paulista de Medicina 124(2): 61-5.

CONTEXT AND OBJECTIVE: Chemotherapy-induced emesis is a limiting factor in treating children with malignancies. Intensive chemotherapy regimens along with emetogenic drug administration have increased the frequency and severity of emesis and nausea. Our study was designed to consider the importance of this problem and the need for improvement in emesis treatment for patients receiving chemotherapy. Our objective was to compare the efficacy and safety of the antiemetic drug granisetron and a regimen of metoclopramide plus dimenhydrinate. DESIGN AND SETTING: Open, prospective and randomized study at Instituto de Oncologia Pediatrica, Department of Pediatrics, Universidade Federal de Sao Paulo. METHODS: From February to August 1994, 26 patients (mean age: 14 years) with osteosarcoma received 80 chemotherapy cycles of iphosphamide (2,500 mg/m²) plus epirubicin (75 mg/m²) or carboplatin (600 mg/m²), or epirubicin (75 mg/m²) plus carboplatin (600 mg/m²). Eighty chemotherapy treatments were analyzed regarding nausea and vomiting control. Patients were randomized to receive either a single dose of granisetron (50 microg/kg) or metoclopramide (2 mg/kg) plus dimenhydrinate (5 mg/kg infused over eight hours). Emesis and nausea were monitored for 24 hours by means of the modified Morrow Assessment of Nausea and Emesis. Statistical analysis utilized the chi-squared, Student t and Mann-Whitney tests, plus data exploration techniques. RESULTS: 62.5% of the patients undergoing chemotherapy responded completely to granisetron, whereas 10% responded to metoclopramide plus dimenhydrinate (p < 0.0001). No severe adverse reactions were found in either of the treatments given. CONCLUSION: In children and adolescents with osteosarcoma, granisetron was safe and more efficient than metoclopramide plus dimenhydrinate for controlling chemotherapy-induced emesis and nausea.

Schmoll, H. J., M. S. Aapro, et al. (2006). "Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment." Annals of Oncology 17(6): 1000-6.

BACKGROUND: We compared an aprepitant regimen with a control regimen of ondansetron + dexamethasone given for 4 days. PATIENTS AND METHODS: Patients scheduled to receive cisplatin > or =70 mg/m² were randomized to either the aprepitant regimen (aprepitant, ondansetron and dexamethasone on day 1; aprepitant and dexamethasone on days 2-3; dexamethasone on day 4) or control regimen (ondansetron + dexamethasone on days 1-4). Patients recorded vomiting, nausea and rescue therapy use. The primary end point was complete response (no vomiting and no use of rescue therapy) in the overall phase (days 1-5 post-cisplatin). RESULTS: Complete response rates were higher in the aprepitant than control group in the overall (72% versus 61%; P = 0.003), acute (day 1; 88% versus 79%; P = 0.005) and delayed phases (days 2-5; 74% versus 63%; P = 0.004), as were rates of no vomiting (overall 77% versus 62%, P < or = 0.001; acute 89% versus 81%, P = 0.004; delayed 79% versus 64%, P < or = 0.001). Rates of no rescue therapy were similar between groups. CONCLUSIONS: Compared with an antiemetic regimen in which ondansetron + dexamethasone were given for 4 days, the aprepitant regimen was superior in the acute, delayed and overall phases of chemotherapy-induced nausea and vomiting. The aprepitant regimen should be considered a new standard of antiemetic therapy for cisplatin-treated patients. www.ClinicalTrials.gov Identifier: NTC00090207.

Subramaniam, K., M. P. Pandia, et al. (2007). "Scheduled prophylactic ondansetron administration did not improve its antiemetic efficacy after intracranial tumour resection surgery in children." European Journal of Anaesthesiology 24(7): 615-9.

BACKGROUND AND OBJECTIVE: Postoperative nausea and vomiting after craniotomy may increase intracranial pressure and morbidity in children. This prospective, randomized, placebo-controlled and double-blinded study was designed to evaluate the antiemetic efficacy of prophylactic ondansetron after intracranial tumour resections in children. **METHODS:** Ninety children were divided into three groups and received saline (Group 1), ondansetron 150 microg kg⁻¹ intravenously at dural closure (Group 2) or two doses of ondansetron 150 microg kg⁻¹ intravenously, the second dose repeated after 6 h (Group 3). Episodes of nausea, emesis and side-effects were noted for 24 h postoperatively. **RESULTS:** Overall 24 h incidence of postoperative nausea and vomiting was not significantly different among the three groups (9 (37.5%) in Group 1 vs. 7 (27%) in Group 2 and 8 (32%) in Group 3, P = 0.73). No difference in rescue antiemetic treatment or postoperative nausea and vomiting at specific time intervals (0-6 and 6-24 h postoperative period) was seen among the three groups. No significant side-effects were noted in any of the three groups. **CONCLUSIONS:** Ondansetron, in this study of 90 children, was not very effective in preventing nausea and vomiting after neurosurgical operations.