

Cancer Care Ontario Practice Guidelines Initiative

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Use of 5-HT₃ receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy

Practice Guideline Report #12-3

ORIGINAL GUIDELINE: March 7, 2000

MOST RECENT LITERATURE SEARCH: January 2003

NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2003

New evidence found by update searches since completion of the original guideline is consistent with the recommendations below.

SUMMARY

Guideline Questions

1. Are the 5-HT₃ receptor antagonists ondansetron, granisetron and dolasetron equivalent in terms of efficacy and adverse effects?
2. Should 5-HT₃ receptor antagonists be administered for more than 24 hours following chemotherapy to prevent delayed-onset emesis?

Target Population

- These recommendations apply to adult cancer patients receiving moderately or highly emetogenic chemotherapy.
- Current standard antiemetic therapy for patients receiving moderately to highly emetogenic chemotherapy includes the use of a 5-HT₃ receptor antagonist and dexamethasone for the first 24 hours following chemotherapy.

Recommendations

- Intravenous dolasetron, granisetron and ondansetron should be regarded as equally efficacious and well tolerated.
- As a first-line approach, 5-HT₃ receptor antagonists should be administered for 24 hours following chemotherapy.
- There are insufficient data to draw conclusions about the equivalence of the 5-HT₃ receptor antagonists when given orally. A single study comparing dolasetron and ondansetron suggests that a higher than recommended dose of oral dolasetron is at least as efficacious as oral ondansetron.

Methods

The literature was searched using MEDLINE (1966 through January 2003), CANCERLIT (1983 through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, the National Guideline Clearinghouse, and abstracts published in annual meeting proceedings of the American Society of Clinical Oncology (1995-2002). Article bibliographies and personal files were also searched to January 2003 for evidence relevant to this practice-guideline report.

Evidence was selected and reviewed by a medical oncologist, members of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Systemic Treatment Disease Site Group (ST DSG) and methodologists. This practice guideline has been reviewed and approved by the ST DSG, which comprises medical oncologists, pharmacists and one community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC). The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

- When 5-HT₃ receptor antagonists are administered for more than 24 hours, the results of a meta-analysis indicate a small (4.1%) decrease in the absolute proportion of patients with delayed-onset emesis.
- A randomized trial showed no advantage when prolonged ondansetron administration was compared with metoclopramide 20 mg orally four times daily.
- No studies have compared the same 5-HT₃ receptor antagonist when given by the oral versus the intravenous route. Two studies of high-dose intravenous ondansetron versus oral granisetron suggest that the recommended dose of the latter is effective and may be regarded as equivalent to administration by the intravenous route.

UPDATE

- Two clinical practice guidelines (1u,2u), two meta-analyses (3u,4u), and four double-blind randomized controlled trials (5u-8u) were identified in the update search and were eligible for review.
- Two clinical practice guidelines from other practice guideline development groups produced recommendations which were consistent with the recommendations outlined above.
- A meta-analysis of 14 randomized trials (including seven non-blinded trials) did not detect statistically significant differences between granisetron and ondansetron for the prevention of acute or delayed nausea or vomiting for either moderately or highly emetogenic chemotherapy. Another meta-analysis, published in abstract form, with data from 28 randomized controlled trials detected no significant differences in acute or delayed nausea or vomiting between ondansetron, granisetron and tropisetron.

Treatment Alternatives

- Alternative approaches to delayed-onset emesis are the prolonged administration of dexamethasone 4 to 8 mg twice daily, or domperidone 20 mg orally four times daily.

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PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at:
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FULL REPORT

I. QUESTIONS

1. Are the 5-HT₃ receptor antagonists ondansetron, granisetron and dolasetron equivalent in terms of efficacy and adverse effects?
2. Should 5-HT₃ receptor antagonists be administered for more than 24 hours following chemotherapy to prevent delayed-onset emesis?

II. CHOICE OF TOPIC AND RATIONALE

A 5-HT₃ receptor antagonist plus dexamethasone has become the conventional antiemetic practice for chemotherapy that is judged to be moderately to highly emetogenic (1). Moderately emetogenic chemotherapeutic regimens are defined as those that induce emesis in 10% to 30% of patients (1). Highly emetogenic regimens are those that cause emesis in at least 30% of patients. Highly emetogenic regimens can be further categorized into those that contain cisplatin, which cause emesis in more than 99% of patients, and those that do not contain cisplatin, which cause emesis in 30% to 90% of patients (1).

Currently, there are four 5-HT₃ receptor antagonists: ondansetron, granisetron, dolasetron and tropisetron. Of these four agents, only ondansetron, granisetron and dolasetron are available commercially in Canada. The factors that should determine which one is selected include efficacy, adverse effects, convenience and cost. The comparison among these drugs will focus on efficacy and adverse effects, since cost will vary depending on the purchasing arrangement, and the recommended schedules for all three agents include dosing no more than twice daily.

Nausea and emesis due to chemotherapy may continue for up to several days following the administration of chemotherapy. Although the antiemetic efficacy of 5-HT₃ receptor antagonists in the first 24 hours following chemotherapy is well established, there is less certainty about their effects beyond 24 hours (1). It has, however, been common practice to administer these agents for up to 48 hours. Since 5-HT₃ receptor antagonists are costly compared to alternative antiemetics, it is desirable to evaluate the extent to which administration beyond the first 24 hours improves control of nausea and vomiting.

III. METHODS

Guideline Development

This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle¹. Evidence was selected and reviewed by a medical oncologist, one member of the CCOPGI's Systemic Treatment DSG, and methodologists. Members of the Systemic Treatment DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of 5-HT₃ receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy, developed through systematic reviews and evidence synthesis. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the guideline report was obtained from the Practice Guidelines Coordinating Committee.

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The Practice Guidelines Development Cycle: A conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.

Literature Search Strategy

The MEDLINE and CANCELIT databases were originally searched from January 1987 to November 1997. This search was updated in November 1998, April 1999 and October 1999. The search terms included the medical subject headings (MeSH) ondansetron, granisetron, neoplasms, practice guidelines, meta-analysis, randomized controlled trials, double-blind and single-blind method; and the text words ondansetron, granisetron, dolasetron, tropisetron, 5HT3 antagonist(s), serotonin antagonist(s), randomized controlled trial and random (truncated). The search also included the publication types practice guideline, meta-analysis and randomized controlled trial. The Physician Data Query (PDQ), the Cochrane Library and the proceedings of the annual meeting of the American Society of Clinical Oncology (ASCO) (1995-1999) were also searched for reports of new or ongoing trials. The lead author checked his personal files for reports of relevant studies. Articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials.

UPDATE

The original literature search has been updated using MEDLINE (through January 2003), CANCELIT (through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, the National Guideline Clearinghouse, and abstracts published in annual meeting proceedings of the American Society of Clinical Oncology (through 2002). Article bibliographies and personal files were also searched to January 2003 for evidence relevant to this practice guideline report.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Reports of randomized trials comparing one or more 5-HT₃ receptor antagonist (dolasetron, granisetron, ondansetron or tropisetron) with a suitable control group (placebo or antiemetic) in adult cancer patients receiving moderately or highly emetogenic chemotherapy.
2. Since emesis and nausea are subjective endpoints, only the results of randomized double-blind studies were used to formulate the recommendations of this guideline. The results of unblinded or single-blind studies are listed in a separate table in Appendix 1.
3. It has been demonstrated that antiemetics used prior to chemotherapy influence the frequency of delayed-onset emesis (2). Therefore, to address the question of duration of administration of 5-HT₃ receptor antagonists, this overview includes only those studies in which the same antiemetics were administered in both the treatment group and the control group during the first 24 hours, or those in which randomization occurred 24 hours after the initial antiemetic therapy.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.
4. Studies where different 5-HT₃ antagonists were used during the first 24 hours were ineligible.

Selecting Trial Outcomes

Investigators have expressed the outcomes of antiemetic studies in several ways including the proportion of patients without emesis, proportion of patients without nausea, proportion of patients without nausea or vomiting, mean number of episodes of vomiting, mean nausea severity and quality of life. In addition, for each measure, the time frame may vary from the first 24 hours to seven days following the administration of chemotherapy. Although various measures of nausea and vomiting are likely to be highly correlated, conclusions may differ when statistical tests show differences of borderline significance. For the purposes of this overview, the proportion of patients without vomiting in the first 24 hours following the administration of chemotherapy was regarded as the primary efficacy

endpoint for comparisons among 5-HT₃ receptor antagonists. This was recorded in virtually all studies and is a clinically relevant outcome. Nausea was recorded in the trials as either the proportion of patients without nausea in the first 24 hours following chemotherapy, or as a mean score according to a visual analogue scale that ranged from “no nausea” (0 mm) to “nausea as bad as it can be” (100 mm). For evaluation of the benefit of prolonged administration of these antiemetics, the same outcome measures were selected.

Synthesizing the Evidence

The intent was to combine (i.e., pool) data from all eligible trials in order to calculate overall estimates of treatment efficacy. Pooled results were expressed as a risk ratio (RR) with a 95% confidence interval (CI). The risk ratio is the proportion of patients in the experimental group, relative to the proportion of patients in the control group, who are likely to experience the event. When the event measured is unfavourable (e.g. emesis), estimates greater than 1.0 favour the control group (e.g. placebo, no antiemetic) and estimates less than 1.0 favour the experimental group (antiemetic therapy). The proportion of patients experiencing emesis was extracted from the trials investigating the efficacy of 5-HT₃ receptor antagonists in delayed-onset emesis and pooled using the fixed effects model. The fixed effects model was used for the meta-analysis because there were too few studies to estimate random effects. The Q-test was used to measure the quantitative heterogeneity among study results. Calculations for the meta-analysis were performed on a Pentium PC using the software program, Metaanalyst0.988, provided by Dr. Joseph Lau (Boston, MA).

IV. RESULTS

Literature Search Results

Twelve double-blind randomized controlled trials (RCTs) addressing the question of the relative efficacy and adverse effects of ondansetron, dolasetron and granisetron were eligible for inclusion in this guideline report (3-14). Nine additional double-blind randomized studies addressed the value of the administration of these agents beyond the first 24 hours (9,15-22). The eligible studies are categorized in Table 1.

An additional double-blind study (23), which randomized patients to receive either ondansetron or low-dose metoclopramide, is discussed at the conclusion of the section, Efficacy of Continuing 5-HT₃ Receptor Antagonists Beyond 24 Hours. Six studies of unblinded or single-blind design were identified and are summarized in Appendix 1 (24-29).

Table 1. Double-blind randomized trials included in this guideline report.

Comparisons	Number of studies	Reference numbers	Summary of results
<i>First 24 hours after chemotherapy:</i> - IV ondansetron v. oral granisetron - IV ondansetron v. IV granisetron - IV or oral ondansetron v. IV granisetron	2 5 1	4,14 3, 5, 6, 10, 11 9	Table 2
<i>First 24 hours after chemotherapy:</i> - IV dolasetron v. IV granisetron - oral dolasetron v. oral ondansetron - IV dolasetron v. IV ondansetron	1 1 2	13 12 7, 8	Table 3
<i>Beyond 24 hours after chemotherapy:</i> - granisetron v. placebo - ondansetron v. placebo - dolasetron v. ondansetron v. placebo - tropisetron v. placebo	2 6 1 1	15, 16 9, 17-20 21 22	Table 4

Relative Efficacy and Toxicity of Ondansetron, Granisetron and Dolasetron

Ondansetron versus Granisetron

Eight large randomized trials have compared ondansetron with granisetron: four with cisplatin chemotherapy (3,6,11,14), three with moderately emetogenic chemotherapy (4,5,9) and one with cisplatin or ifosfamide (10). These are summarized in Table 2. All studies concluded that there were no statistically significant differences between the antiemetic agents with respect to preventing nausea or vomiting in the first 24 hours after administration of chemotherapy. In one study (14), the 95% confidence intervals on the difference in the proportion of patients with emesis did not include zero, raising the possibility of a slight superiority of ondansetron 32 mg intravenously over granisetron 2 mg orally, but two other studies of similar design failed to detect a difference (4,5).

Both of these agents are well tolerated. Two studies (4,5) found that abnormal vision was more frequently associated with ondansetron than with granisetron and one study found a higher frequency of dizziness with ondansetron (4). The observation, in another study described below, of a higher incidence of these adverse effects with ondansetron in comparison with dolasetron (8) suggests that ondansetron is associated with a slightly different adverse effect profile than the comparators. These adverse effects, however, have not been problematic in practice with the lower doses of ondansetron that are used in Canada.

Dolasetron versus Either Ondansetron or Granisetron

Four studies have compared intravenous (\pm oral) dolasetron with either ondansetron (7,8,12) or granisetron (13). These studies are summarized in Table 3. With one exception, these studies demonstrate no evidence of differences between dolasetron and the other two antiemetics. The exception was a trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) (8). In that study, the proportion of patients free of emesis after 24 hours was significantly lower in patients who received 2.4 mg/kg (approximately 170 mg for a 70 kg patient) of dolasetron as compared with ondansetron. This observation may have little clinical relevance because there was no difference in efficacy after seven days had elapsed and two other studies (7,13) suggest that the intravenous dose of 2.4 mg/kg of dolasetron may be inferior to the lower dose of 1.8 mg/kg dose. The latter dose is closer to conventional treatment (7,13).

With respect to adverse effects, three studies noted that asymptomatic electrocardiographic changes (PR, QRS and QT interval prolongation) were more common with dolasetron than with granisetron (13) or ondansetron (7,8). These changes were judged to be clinically insignificant. In the three studies that used what is now the recommended intravenous or oral dose of dolasetron, there were no significant differences noted in other adverse effects (7,8,12). A study that used a higher than recommended dose of dolasetron, 2.4 mg/kg intravenously followed by 200 mg orally per day, observed that constipation, abnormal vision and dizziness were significantly less common with dolasetron than with ondansetron, whereas diarrhea was more common (8).

Table 2. Double-blind randomized trials comparing ondansetron and granisetron.

1st Author (ref), year	# Rand. (# eval)	Chemotherapy	Treatment groups (5-HT3 antagonist given on day of chemotherapy)	Rates of control of:	
				vomiting	nausea
Gralla (14) 1998	1054 (1054)	Cisplatin	Ondansetron 32 mg IV Granisetron 2 mg p.o.	67% 61% (95% CI on difference: -11.7, -0.1)	59% 55%
Italian group (3) 1995	973 (966)	Cisplatin	Ondansetron 8 mg IV Granisetron 3 mg IV	79% 80%	72% 72%
Navari (11) 1995	994 (987)	Cisplatin	Ondansetron 0.15 mg/kg IV X3 Granisetron 10 □g/kg IV X1 Granisetron 40 □g/kg IV X1	51% 47% 48%	40% 39% 42%
Noble (10) 1994	359 (309) cross-over	Cisplatin or ifosfamide	Ondansetron 24 mg IV Granisetron 3 mg IV	91% 95% (cycle 1)	NR
Perez (4) 1998	1085 (1085)	Cyclophosphamide or carboplatin	Ondansetron 32 mg IV Granisetron 2 mg p.o.	73% 71%	58% 60%
Perez (5) 1998	623 (573) cross-over	AC+F*	Ondansetron 32 mg IV Granisetron 10 µg/kg IV	63% 59%	49% 44%
Ruff (6) 1994	497 (496)	Cisplatin	Ondansetron 8 mg IV Ondansetron 32 mg IV Granisetron 3 mg IV	59% 51% 56%	56% 48% 56%
Stewart (9) 1995	514 (488)	Cyclophosphamide-containing regimens	Ondansetron 8 mg IV Ondansetron 8 mg p.o. Granisetron 3 mg IV	78% 78% 81%	51% 55% 54%

NOTE: eval = evaluable; IV = intravenously; NR = not reported; p.o. = orally; rand. = randomized.

* cyclophosphamide/doxorubicin + 5-fluorouracil

Table 3. Double-blind randomized trials comparing dolasetron versus either ondansetron or granisetron.

1 st Author (ref), year	# Rand. (# eval.)	Chemotherapy	Treatment groups (5-HT ₃ antagonist given on day of chemotherapy)	Rates of control of:	
				vomiting	nausea
Audhuy (13) 1996	476 (474)	Cisplatin	Dolasetron 1.8 mg/kg IV Dolasetron 2.4 mg/kg IV Granisetron 3 mg IV	54% 47% 48%	mean score = 34 38 36
Fausser (12) 1996	399 (398)	Moderately emetogenic	Dolasetron 25 mg p.o. Dolasetron 50 mg p.o. Dolasetron 100 mg p.o. Dolasetron 200 mg p.o. Ondansetron 8 mg p.o. X 3 or 4	45% 49% 61% 76% 72%	median change score* = 29 31 4 0 3
Hesketh (7) 1996	609 (609)	Cisplatin	Dolasetron 1.8 mg/kg IV Dolasetron 2.4 mg/kg IV Ondansetron 32 mg IV	44% 40% 43%	median score = 10 22 16
Lofters (8) 1997	703 (696)	Moderately emetogenic	Dolasetron 2.4 mg/kg IV Ondansetron 32 mg IV	57% 67% (p=0.013)	mean score = 10 13 (p=0.051)

NOTE: eval. = evaluable; rand. = randomized;

*change from baseline score (measured before chemotherapy) on a visual analogue scale where 0 = "no nausea" and 100 = "nausea as bad as it could be". Lower differences from baseline indicate less severe nausea.

Efficacy of Continuing 5-HT₃ Receptor Antagonists Beyond 24 Hours

Nine studies, summarized in Table 4, randomized patients to receive either a 5-HT₃ receptor antagonist or placebo beyond 24 hours (9,15-22). Four of these studies also administered dexamethasone to all patients beyond day one (15,16,19,22).

The study by Gandara and colleagues enrolled only 50 patients and was therefore too small to rule out the possibility of a clinically important difference (20). Two studies (17,18) were designed to evaluate the effect of continuing 5-HT₃ receptor antagonists beyond the first 48 hours after chemotherapy, but the published reports did not present the data for these patient groups in a way that could be compared with the patient group that received placebo after 48 hours. In the study by Stewart et al (9), the administration of granisetron in the first 24 hours was compared with the administration of ondansetron for more than 24 hours. Since an analysis of ondansetron versus granisetron showed no difference in their efficacy during the first 24 hours (3-6,9-11,14), this could be regarded as another trial of short versus prolonged 5-HT₃ receptor antagonist administration.

The data from two studies suggested that 5-HT₃ receptor antagonists have a clinically important impact on the delayed-onset of emesis (17,19). A study by the NCIC CTG (19) showed an absolute improvement of 18% in the rate of complete control of emesis with ondansetron over the five days following moderately emetogenic chemotherapy (60% v. 42%; p=0.012) when compared to placebo. Similar results have been found in patients receiving high-dose cisplatin. In the study by Navari and colleagues (17), there was an absolute difference of borderline significance in the complete response rate with ondansetron compared with placebo from 24 to 72 hours after chemotherapy (36% v. 26%; p=0.064). Thus, two studies support the

possibility that 5-HT₃ receptor antagonists may show clinically important benefits when administered beyond the first 24 hours.

Four studies failed to detect a statistically significant improvement in delayed-onset emesis or nausea with prolonged administration of 5-HT₃ receptor antagonists. In patients receiving high-dose cisplatin, Olver and colleagues (18) found that the same schedule of ondansetron given to the same population of patients as in the study by Navari and colleagues, produced no significant benefit when compared to placebo (a 5% difference in protection from emesis in favour of ondansetron on either day two to three or day two to six, p value not significant). An NCIC CTG study in patients receiving high-dose cisplatin found identical results with granisetron or placebo given to prevent delayed-onset emesis and nausea (15). In a study of similar design, Goedhals and colleagues (16) found no advantage to continuing administration of granisetron. Sorbe and colleagues (22) failed to demonstrate benefit with use beyond 48 hours in a study of tropisetron, a 5-HT₃ receptor antagonist that is not commercially available.

An NCIC CTG study (21) of patients receiving moderately emetogenic chemotherapy concluded that there was no statistically significant improvement in the complete response rate at seven days when either ondansetron plus dexamethasone or dolasetron plus dexamethasone was continued beyond the first 24 hours when compared to dexamethasone alone (47% versus 41% in favour of continuation, p=0.24). There was, however, a statistically significant improvement in the mean severity of nausea (p=0.015) in favour of 5-HT₃ antagonists.

One additional study of potential relevance was a comparison of ondansetron with low-dose metoclopramide in patients receiving high-dose cisplatin (23). There was a 2% difference in the rate of complete protection from emesis. The authors concluded that metoclopramide and ondansetron were equally effective in preventing delayed-onset emesis. However, since metoclopramide 20 mg orally four times daily has not been tested against placebo, it may also be true that neither was effective.

Table 4. Randomized placebo-controlled trials evaluating 5-HT₃ receptor antagonists beyond 24 hours.

1 st Author (ref), year	# Rand. (# eval)	Chemotherapy	Treatment groups (5-HT ₃ antagonist given up to 7 days after chemotherapy)	Rates of control of:	
				vomiting	nausea
Gandara (20) 1992	50 (50)	Cisplatin	Placebo Ondansetron 16 mg t.i.d. days 1-4	33% 40%	28-44% 53-60% (on days 1 to 4)
Latreille (15) 1998	447 (435)	Cisplatin	Placebo Granisetron 1 mg b.i.d. days 2-7	36% 37%	27% 23%
Navari (17) 1995	538 (538)	Cisplatin	Placebo Ondansetron 8 mg b.i.d. days 2-3 Ondansetron 8 mg b.i.d. days 2-6	26% 36%† (p=0.064)	19% 21%#
Olver (18) 1996	604 (604)	Cisplatin	Placebo Ondansetron 8 mg b.i.d. days 2-3 Ondansetron 8 mg b.i.d. days 2-6	49% 54%†	34% 35%†
Pater (21) 1997 (NCIC CTG)	407 (402)	Moderately emetogenic	Placebo Ondansetron 8 mg b.i.d. days 2-7 Dolasetron 200 mg days 2-7	41% 47%‡	mean score* =9 6‡ (p=0.015)
Stewart (9) 1995	514 (488)	Cyclophosphamide -containing regimens	Placebo Ondansetron 8 mg b.i.d. days 2-5	54% 58% (day 1-5)	25% 33% (day 1-5) (p=0.009)
Kaizer (19) 1994 (NCIC CTG)	302 (295)	Moderately emetogenic	Placebo Ondansetron 8 mg b.i.d. days 2-5	42% 60% (p=0.012)	mean score* = 19 9 (p=0.002)
Sorbe (22) 1998	300 (282)	Cisplatin	Placebo Tropisetron 5 mg days 2-6	72% 77%	41% 42%
Goedhal s (16) 1998	654 (619)	Cisplatin	Placebo Granisetron 1 mg b.i.d. days 2-6	58% 57%	43% 40%

NOTE: b.i.d. = twice daily; eval. = evaluable; IGAR = Italian Group for Antiemetic Research; rand. = randomized; t.i.d. = three times daily

* lower score = less severe nausea

† day 2-3, ondansetron groups combined

‡ 5-HT₃ groups combined

§ patients who did not have either vomiting or moderate-to-sever nausea in the first 24 hours after chemotherapy

¶ patients who had vomiting and/or moderate-to-sever nausea in the first 24 hours after chemotherapy

day 2-3, data estimated from graphs

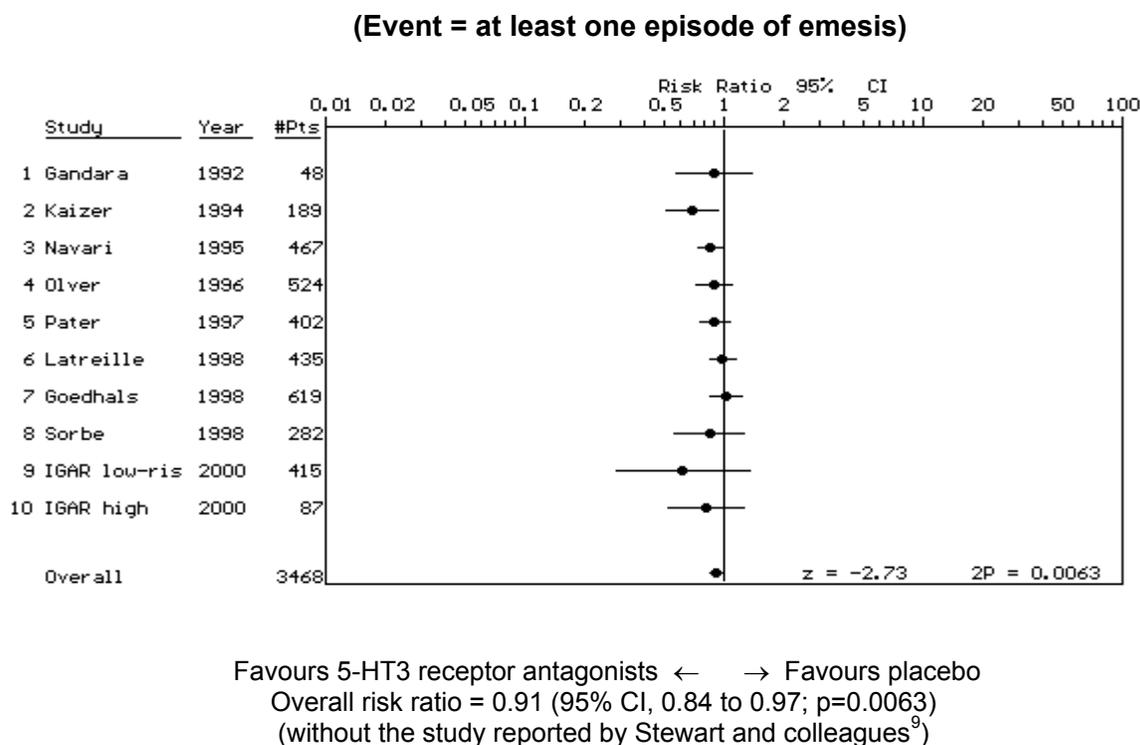
Pooled Analysis

Consensus among DSG members could not be reached about whether or not to include the study of granisetron in the first 24 hours versus ondansetron for more than 24 hours, by Stewart and colleagues (9), in the meta-analysis. This is because the study groups received different 5-HT₃ receptor antagonists during the first 24 hours. An analysis with and without the inclusion of the study by Stewart et al (9) is presented.

Although there was variation among trial results in terms of statistical significance, six of eight placebo-controlled trials showed differences that favoured continuing the 5-HT₃ receptor antagonist beyond 24 hours. When data based on 2966 patients from eight trials were combined, there was a difference between groups (RR = 0.92; 95% CI, 0.85 to 0.98; p=0.016). Inclusion of the study by Stewart and colleagues, marginally increased the effect size (RR=0.91, 95% CI, 0.85 to 0.98, p=0.0072).

The results of the meta-analysis can also be expressed in terms that may be more clinically relevant. Administering a 5-HT₃ receptor antagonist for more than 24 hours was associated with an absolute improvement of 4.6% in the complete response rate. Alternatively, 22 patients would have to be treated with prolonged 5-HT₃ receptor antagonist administration in order to completely prevent emesis in one additional patient. The magnitude of the benefit, while statistically significant, is small.

Figure 1 (updated). Risk ratios from randomized placebo-controlled trials evaluating antiemetic use beyond 24 hours after chemotherapy.



Toxicity

With respect to adverse effects, four studies found that there was more constipation associated with continuing the use of 5-HT₃ receptor antagonists beyond 24 hours following chemotherapy (15-18).

Quality of Life

None of the four studies that measured quality of life detected a difference in global scores of patient well-being between groups of patients treated with a 5-HT₃ receptor antagonist and those who received placebo (9,15,19,21).

Dose, Schedule and Route of Administration

The dose, frequency and route of administration varied widely across the studies (Table 5). In theory, this heterogeneity in tested dose, route and schedule might make it difficult to draw conclusions.

Ondansetron

Clinical trials that have established that ondansetron is comparable in efficacy to granisetron and dolasetron have largely used a single 32 mg intravenous (IV) dose. In Canada, however, usual practice would be to administer two to three 8 mg doses of oral ondansetron in the first 24 hours, or an initial 8 mg intravenous dose followed by oral doses. There is some reassurance from the fact that two randomized double-blind trials have concluded that 8 mg IV of ondansetron is equivalent to 32 mg IV (6,30). However, a third study came to different conclusions (31). A recent consensus conference concluded that 8 mg could be regarded as the standard intravenous dose (32). Conclusions derived from a study using a 32 mg dose can, therefore, likely be extrapolated to the use of an 8 mg IV dose. One study suggested that, for moderately emetogenic chemotherapy, 8 mg intravenously plus 8 mg orally 8 hours later was equivalent to all oral administration (9). The evidence suggests that the information gained from studies comparing high-dose ondansetron with granisetron or dolasetron is relevant to a practice in which at least a single intravenous dose of 8 mg is given.

Table 5. Variation in dose and route of administration of ondansetron, dolasetron and granisetron across studies.

Antiemetic	Acute	Delayed
Ondansetron	8 or 32 mg IV X1 (3-8)	8 mg p.o. b.i.d. (9,17-19,21,3u)
	8 mg or 0.15 mg/kg IV X3 (10,11) 8 mg IV then 8 mg p.o. b.i.d. (9) 8 mg p.o. every 8 hrs X3-4 (12)	16 mg p.o. t.i.d. (20)
Granisetron	3 mg IV X1 (13) 2 mg p.o. X1 (4,5,14) 10 or 40 µg/kg IV X1 (11)	1 mg p.o. b.i.d. (15)
Dolasetron	1.8 or 2.4 mg/kg X1 (7,8,13) 25-100 mg p.o. X1 (12)	200 mg p.o. daily (21)

Note: IV = intravenously; p.o. = orally; b.i.d. = twice daily; t.i.d. = three times daily

Granisetron

For granisetron, the most commonly studied dose is 3 mg intravenously, yet the recommended dose is 1 mg. Based upon evidence from randomized trials, a consensus conference concluded that 1 mg given intravenously provides maximum antiemetic protection (32). There was only moderate confidence that granisetron 2 mg orally could be considered the standard dose. After the consensus conference was conducted, three large double-blind studies were published, showing that this dose was equivalent to ondansetron 32 mg given intravenously (4,5,14). Thus for both ondansetron and granisetron, the heterogeneity of tested doses probably has little impact on the validity of the comparisons and their extrapolation to clinical practice.

Dolasetron

For dolasetron, the comparability of clinical trials to clinical practice is slightly more complex. There is evidence from pooled studies that when administered intravenously, 100 mg is the optimal dose (33). However, in oral dosing studies, two reports have suggested that 200 mg is more effective than 100 mg (12,34), whereas another study concluded that 100 mg provided

results that were as effective as 200 mg (35). The two studies comparing oral dolasetron with granisetron or ondansetron used a 200 mg dose whereas the recommended dose is 100 mg. For this reason, it is not clear that the results from oral dolasetron trials can be extrapolated well to clinical practice.

UPDATE

Two clinical practice guidelines (1u,2u), two meta-analyses (3u,4u), and four double-blind randomized controlled trials (5u-8u) were identified in the update search and were eligible for review.

Practice Guidelines

The American Society of Clinical Oncology (ASCO) and the American Society of Health System Pharmacists (ASHP) developed evidence-based recommendations on the use of antiemetics (1u,2u). Both groups produced recommendations which were consistent with the recommendations outlined in this practice guideline report.

Meta-Analyses

Two meta-analyses were located in the update search of the literature (3u,4u). del Giglio et al (3u) pooled data from published reports or abstracts of 14 randomized trials of ondansetron versus granisetron for the prevention of acute and delayed nausea and vomiting induced by highly or moderately emetogenic chemotherapy. Trials published between 1990 and May 1999, with more than 25 patients per arm, were found by a systematic search of Medline and CancerLit.

This meta analysis (1u) included seven of eight double-blind trials included in the ST DSG original practice guideline (3,4,6,9-11,14) plus seven non-blinded trials that were not eligible for the guideline report. One cross-over trial that was included in the practice guideline (5) was ineligible for the meta-analysis by del Giglio et al because data could not be extracted for the first cycle of treatment before crossover. The published meta-analysis did not detect statistically significant differences between granisetron and ondansetron in rates of acute or delayed nausea or vomiting for either moderately or highly emetogenic chemotherapy.

The second meta-analysis published as an abstract by Barrajon et al (4u), pooled data from 28 randomized studies that compared granisetron or tropisetron to ondansetron for the prevention of acute or delayed nausea and vomiting. There were no significant results in acute or delayed nausea or vomiting between ondansetron, granisetron and tropisetron.

Double-Blind Randomized Trials

Four double-blind randomized trials were located in the update search of the literature (5u-8u).

The double-blind randomized crossover trial with 136 patients by Barrajon et al (5u) comparing ondansetron, granisetron, and tropisetron, detected no significant differences in the incidence of acute or delayed nausea and vomiting between any of the three drugs. Patients did however report an overall preference for ondansetron.

A study by the Italian Group for Antiemetic Research (IGAR) (6u) of patients receiving moderately emetogenic chemotherapy concluded that ondansetron did not add to the antiemetic efficacy of dexamethasone in the group of patients with no vomiting or moderate-to-severe nausea in the first 24 hours after chemotherapy (low-risk) when ondansetron plus dexamethasone was compared with dexamethasone alone (complete response rate, 91.8% v. 87.4%). In the group of patients who did vomit or experience moderate-to-severe nausea in the first 24 hours after chemotherapy (high-risk), there was a numerically large benefit (17.6%) in the complete response rate in patients receiving ondansetron plus dexamethasone compared with patients receiving dexamethasone alone, but the difference was not statistically significant. A higher proportion of patients in the low-risk group who were taking ondansetron and

dexamethasone experienced greater constipation than those taking dexamethasone alone (25% v. 8.75; $p < 0.001$).

The results of the IGAR study (6u) were added to the original meta-analysis. The proportion of patients experiencing emesis in both the high and low-risk groups were added, for a total of nine studies with ten comparisons (Figure 1). When data based on 3468 patients from nine trials were combined, there was a difference between groups (RR=0.91; 95% CI, 0.84 to 0.97; $p=0.0063$). Adding the study by Stewart and colleagues marginally increased the effect size (RR=0.90, 95% CI, 0.84 to 0.97; $p=0.0028$).

A trial by de Wit et al (7u) compared granisetron to ondansetron. Patients on prophylactic ondansetron plus dexamethasone who had experienced vomiting or moderate-to-severe nausea within 24 hours of chemotherapy with cisplatin- or cyclophosphamide-based chemotherapy were randomized to continue treatment with intravenous ondansetron plus dexamethasone or to receive intravenous granisetron plus dexamethasone. The trial was double-blind. Nine of 19 patients in the granisetron group had complete protection from vomiting and nausea after randomization, in contrast to one of 21 on ondansetron ($p=0.005$).

The randomized trial by Appro et al (8u), reported as an abstract, compared granisetron with low-dose metoclopramide, both combined with dexamethasone in the prevention of chemotherapy-induced delayed emesis. There were no significant differences between the two antiemetic agents in patients experiencing acute or delayed emesis (8u).

V. INTERPRETIVE SUMMARY

When used in optimal doses by the intravenous route, there is strong evidence that ondansetron, granisetron and dolasetron are equally effective in preventing nausea and vomiting. With the exception of granisetron, the evidence is less abundant when these antiemetics are administered orally. Three studies suggest that oral granisetron in a dose of 2 mg appears to be as effective as high-dose intravenous ondansetron and one study suggests that oral ondansetron given twice in 24 hours is as effective as 8 mg given intravenously plus 8 mg orally. There are relatively few studies of oral dolasetron. The recommended dolasetron dose (100 mg) may not provide optimal results. Thus, for oral dosing, the published evidence is strongest for granisetron, although clinical experience suggests that repeated doses of ondansetron provide good antiemetic control in many patients.

The adverse effect profile of all three 5-HT₃ receptor antagonists appears to be similar, apart from a higher frequency of electrocardiographic changes with dolasetron and a higher frequency of dizziness and abnormal vision with high-dose intravenous ondansetron. Since ondansetron, granisetron and dolasetron are all regarded as well tolerated by the vast majority of patients, it is uncertain whether these observed differences have any clinical relevance.

The studies addressing the utility of administering these antiemetics for more than 24 hours to prevent delayed-onset emesis have come to varying conclusions. Although these agents are comparable, only ondansetron has been adequately investigated. Since five of seven studies show at least a 5% improvement in the rate of complete protection from emesis with a statistically significant result when all studies are combined, the most probable conclusion is that these agents do confer a modest benefit. The benefit of administering these agents for several days following chemotherapy, however, is sufficiently small that it has not been routinely detectable in studies of substantial size.

VI. TREATMENT ALTERNATIVES

Alternative approaches to controlling delayed-onset emesis have been evaluated. In the era before selective 5-HT₃ receptor antagonists, metoclopramide 0.5 mg/kg orally four times daily plus diphenhydramine decreased delayed-onset emesis (36). A lower dose of metoclopramide, 20 mg orally four times a day, has been shown to be equivalent to oral ondansetron, 8 mg twice daily, in a large randomized trial, with no reported side effects (23). Metopimazine, a dopamine

receptor antagonist, was superior to placebo in three double-blind randomized trials (37-39). Adverse effects were common with metopimazine, but were generally mild (37-39). Domperidone, 20 mg orally four times a day, was superior to placebo in a small trial, with no reported adverse effects (40). Thus, dopamine receptor antagonists have demonstrated efficacy, with mild or no associated adverse effects, although three of the studies with statistically significant results used an agent that is not commercially available.

In addition to studies suggesting benefit from dopamine receptor antagonists, continuation of dexamethasone beyond the first 24 hours after chemotherapy has also been evaluated. Studies of oral dexamethasone in both the era before and after the availability of 5-HT₃ receptor antagonists have shown results that are superior to no additional treatment (18,36,41). Adverse effects associated with continuation of dexamethasone were mild to non-existent (18,36,41).

The modest incremental benefit of 5-HT₃ receptor antagonists over placebo suggests that prolonged administration should not be considered as a standard first-line approach to prevent delayed-onset emesis. The use of dopamine receptor antagonists and/or dexamethasone appear to be at least as effective as continuing 5-HT₃ receptor antagonists in controlling delayed-onset emesis.

VII. ONGOING TRIALS

Protocol ID(s)

UCLA-9904005, SB-BRL43694A/513, NCI-G00-1674. Phase III Randomized Study of Granisetron in the Prevention of Nausea and Vomiting Following Cyclophosphamide-Based or Carboplatin-Based Chemotherapy in Patients with Malignant Disease.

This trial is a double-blind randomized trial comparing the efficacy and safety of oral granisetron versus placebo in preventing nausea and vomiting during the 48 hours that begins 24 hours after administration of cyclophosphamide-based or carboplatin-based chemotherapy regimens in patients with malignant disease. A total of 434 patients (217 per arm) will be accrued for this study. Date summary last modified: 2000-06-01

VIII. DISEASE SITE GROUP CONSENSUS PROCESS

There was a lengthy discussion among the Disease Site Group members regarding the statistical analysis of the data for delayed-onset emesis. Although prolonged administration of 5-HT₃ receptor antagonists is associated with a statistically significant reduction in the rate of emesis, the difference in absolute terms is very small and the upper limit on the 95% confidence interval on the risk ratio (0.98) approaches 1.0.

There is no accepted standard for clinical as opposed to statistical significance. A similar risk ratio would likely be regarded as important for an endpoint of survival, particularly if the confidence limits were narrow. Unlike many other clinical problems, one could reserve the prescription of prolonged 5-HT₃ receptor antagonists for the minority who experience delayed-onset emesis after the first cycle of chemotherapy. The concept of salvage with second-line therapy has been demonstrated in several antiemetic studies. A cost-effectiveness analysis of this strategy would be ideal but is not possible with the current data.

It was felt that the most prevalent practice was administration of these agents for 48 hours after chemotherapy. Since the 5-HT₃ receptor antagonists are generally well tolerated and there is probably a benefit for a very small number of patients, practitioners may choose not to alter their practice for a majority of their patients. However, administration of these agents for the first 24 hours following chemotherapy should be regarded as an appropriate first-line approach. Limiting administration of these agents to the first 24 hours may be particularly desirable where the financial burden of treatment is of importance, or there is concern about the potential for additional constipation. The alternative drugs that have been shown to reduce delayed-onset emesis (dexamethasone and dopamine receptor antagonists) are less costly than 5-HT₃ receptor antagonists.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Practice Guideline

Based on the evidence contained under the Original subtitles throughout this report, the ST DSG drafted the following recommendations:

Draft Recommendations

The following recommendations apply to cancer patients receiving moderately or highly emetogenic chemotherapy:

- Standard antiemetic therapy for patients receiving moderately to highly emetogenic chemotherapy includes the use of a 5-HT₃ receptor antagonist for the first 24 hours following chemotherapy.
- Intravenous dolasetron, granisetron and ondansetron should be regarded as equally efficacious and well tolerated.
- No studies have compared different 5-HT₃ receptor antagonists given orally. Indirect evidence, from trials where one of these agents was given by the intravenous route and the other was administered orally, suggests that the recommended oral doses of granisetron and ondansetron produce equivalent benefits.
- As a first-line approach, 5-HT₃ receptor antagonists should be administered for 24 hours following chemotherapy.
- When 5-HT₃ receptor antagonists are administered for more prolonged periods, there is a small (4.6%) decrease in the proportion of patients with delayed-onset emesis. A randomized trial showed no advantage when prolonged ondansetron administration was compared with metoclopramide 20 mg orally four times daily. Alternative approaches to delayed-onset emesis are the prolonged administration of dexamethasone 4 to 8 mg twice daily or domperidone 20 mg orally four times daily.

Practitioner Feedback

Based on the evidence contained in the original guideline report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 150 practitioners in Ontario (100 medical oncologists and 50 pharmacists). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Systemic Treatment Disease Site Group.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 6. Seventy-eight (56%) surveys were returned. Seventy-two (92%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey.

Table 6. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the <i>Choice of Topic</i> section of the report, is clear.	71 (97)	2 (3)	0 (0)
There is a need for a clinical practice guideline on this topic.	66 (90)	6 (9)	1 (1)
The literature search is relevant and complete.	62 (91)	5 (8)	1 (1)
The results of the trials described in the report are interpreted according to my understanding of the data.	64 (93)	2 (3)	3 (4)
The draft recommendations in this report are clear.	59 (82)	10 (14)	3 (4)
I agree with the draft recommendations as stated.	60 (83)	6 (9)	6 (8)
This report should be approved as a practice guideline.	55 (76)	12 (17)	5 (7)
If this report were to become a practice guideline, how likely would you be to make use of it in you own practice?	Not at all likely or unlikely	Unsure	Very likely or likely
	4 (6)	10 (15)	55 (79)

Summary of Main Findings

Forty (56%) respondents provided written comments. The main points are summarized below.

1. There were requests for specific dose recommendations for 5-HT3 receptor antagonists.
2. One practitioner felt that the meta-analysis should be redone by pooling only the studies comparing ondansetron to placebo.
3. There was a concern that the variability of dose and schedule of 5-HT3 receptor antagonists in the studies meant that conclusions involve extrapolation of the data.
4. One practitioner voiced a concern that waiting until the second cycle to use 5-HT3 receptor antagonists for delayed emesis may compromise efficacy due to anticipatory conditioning.
5. There were comments from some practitioners regarding study terminology. Specifically, it was felt that certain studies designated placebo-controlled contained more than placebo.
6. There was a suggestion to provide an analysis of nausea data.
7. Several requests were made to mention the reported adverse effects of the treatment alternatives (e.g. metoclopramide).
8. One practitioner expressed confusion over conflicting evidence regarding the recommended dose of oral dolasetron.
9. There was a request for data on partial response to be included in the report.
10. One practitioner requested a subgroup analysis for high-dose chemotherapy/transplantation.
11. Requests were made to emphasize the role of dexamethasone in antiemetic therapy.
12. There were suggestions to define moderate to highly emetogenic chemotherapy regimens.
13. One respondent requested cost information other than a cost per tablet.

Modifications/Actions

1. The consensus of the STDSG was that this guideline was only intended to address the evidence regarding the relative efficacy of ondansetron, dolasetron and granisetron. Recommendations regarding dose, route and frequency are outside of the scope of the guideline.
2. There was no a priori reason for believing that agents that are identical in efficacy for acute onset emesis would differ for delayed-onset emesis, and therefore subgroup analysis was avoided.

3. With the possible exception of oral dolasetron, the schedule and dose within the ranges used in the analysis have not been shown to affect efficacy. Subsequently, no changes have been made to the guideline document in response to this concern.
4. In response to the comment regarding compromised efficacy for delayed emesis, by instituting the antiemetic after the first cycle of chemotherapy, the loss in efficacy is likely to be minimal. The initial favourable results with these agents were seen in pretreated populations. The difference between use and non-use of 5-HT₃ receptor antagonists for delayed-onset emesis in previously untreated patients is less than 5% by the meta-analysis. Therefore, the predicted loss would have to be less than 5%.
5. A statement was added to the Methods section of the report to clarify this concern.
6. Nausea and vomiting are strongly correlated. There is more heterogeneity in the outcome of nausea, and a meta-analysis would involve only a subset of studies. Consequently, a separate analysis for nausea was not performed.
7. Statements regarding reported adverse effects were added to the Treatment Alternatives section to address this suggestion.
8. This issue is already discussed in the Interpretive Summary section of the guideline report.
9. The Systemic Treatment Disease Site Group chose only to look at complete responses. This was done because partial responses tend to be variable in definition, and may or may not be included in reports of a given trial. There was agreement not to look at subsets such as partial response because the numbers are too small.
10. This could not be accomplished, as none of the studies included in the guideline included the transplant population. These studies tend to be small, and are sometimes non-randomized.
11. To address this request, changes were made to the first bullet of the recommendation. A statement was also added to the Choice of Topic and Rationale section, with reference to the antiemetic guidelines produced by the American Society of Clinical Oncology (ASCO).
12. A paragraph was added to the Choice of Topic and Rationale section of the report to define these terms, referencing the ASCO antiemetic guidelines.
13. A table was added to the Policy Implications section to include a per day cost of oral antiemetics.

Approved Practice Guideline Recommendations

This practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the ST DSG and the Practice Guideline Coordinating Committee.

Target Population

- These recommendations apply to adult cancer patients receiving moderately or highly emetogenic chemotherapy.
- Current standard antiemetic therapy for patients receiving moderately to highly emetogenic chemotherapy includes the use of a 5-HT₃ receptor antagonist and dexamethasone for the first 24 hours following chemotherapy.

Recommendations

- Intravenous dolasetron, granisetron and ondansetron should be regarded as equally efficacious and well tolerated.
- As a first-line approach, 5-HT₃ receptor antagonists should be administered for 24 hours following chemotherapy.
- There are insufficient data to draw conclusions about the equivalence of the 5-HT₃ receptor antagonists when given orally. A single study comparing dolasetron and ondansetron

suggests that a higher than recommended dose of oral dolasetron is at least as efficacious as oral ondansetron.

Key Evidence

- When 5-HT₃ receptor antagonists are administered for more than 24 hours, the results of a meta-analysis indicate a small (4.6%) decrease in the absolute proportion of patients with delayed-onset emesis.
- A randomized trial showed no advantage when prolonged ondansetron administration was compared with metoclopramide 20 mg orally four times daily.
- No studies have compared the same 5-HT₃ receptor antagonist when given by the oral versus the intravenous route. Two studies of high-dose intravenous ondansetron versus oral granisetron suggest that the recommended dose of the latter is effective and may be regarded as equivalent to administration by the intravenous route.

Treatment Alternatives

- Alternative approaches to delayed-onset emesis are the prolonged administration of dexamethasone 4 to 8 mg twice daily, or domperidone 20 mg orally four times daily.

X. POLICY IMPLICATIONS

There is currently no policy except at an institutional level as to the 5-HT₃ receptor antagonist of choice. With respect to intravenous administration, a single intravenous dose of ondansetron 8 mg, granisetron 1 mg or dolasetron 100 mg may be regarded as providing similar beneficial and (minor) adverse effects. When used orally, granisetron 2 mg orally once, and probably ondansetron 8 mg orally twice in the first 24 hours provide benefit equivalent to intravenous administration and are thus considered reasonable alternatives. The approved dose of oral dolasetron, however, may not provide optimal antiemetic results and at this dose level cannot be considered to be equivalent to ondansetron and granisetron .

The Ontario Ministry of Health Drug Benefit Formulary (No. 36, September 15, 1999) has stated that the therapeutic value of using these agents more than 24 hours after the last dose of chemotherapy is unproven, but the formulary has no mechanism in place to limit their use to the first 24 hours prior to chemotherapy. The Formulary costs per day of oral agents are listed in Table 7. The costs listed in the table exclude the professional (dispensing) fee. The expense of these agents, the small benefit demonstrated in the meta-analysis, and the effectiveness of dexamethasone and possibly dopamine receptor antagonists, suggest that the first-line approach be limited to the initial 24 hours after chemotherapy. In patients with delayed-onset emesis, prolonged administration of a 5-HT₃ receptor antagonist may benefit a small minority of patients.

Table 7. Per-day cost of oral antiemetic agents (Ontario Drug Benefit Formulary [No. 36, September 15, 1999]).

Agent	Dose	Cost/day (\$ Canadian)
oral dolasetron	100 mg daily	\$26.00
oral granisetron	1 mg twice daily	\$36.00
oral ondansetron	8 mg twice daily	\$36.56
dexamethasone	4 mg twice daily	\$1.54
metoclopramide	20 mg four times daily	\$0.47

XI. PRACTICE GUIDELINE

This practice guideline reflects the most current evidence reviewed by the Systemic Treatment DSG.

Target Population

- These recommendations apply to adult cancer patients receiving moderately or highly emetogenic chemotherapy.
- Current standard antiemetic therapy for patients receiving moderately to highly emetogenic chemotherapy includes the use of a 5-HT₃ receptor antagonist and dexamethasone for the first 24 hours following chemotherapy.

Recommendations

- Intravenous dolasetron, granisetron and ondansetron should be regarded as equally efficacious and well tolerated.
- As a first-line approach, 5-HT₃ receptor antagonists should be administered for 24 hours following chemotherapy.
- There are insufficient data to draw conclusions about the equivalence of the 5-HT₃ receptor antagonists when given orally. A single study comparing dolasetron and ondansetron suggests that a higher than recommended dose of oral dolasetron is at least as efficacious as oral ondansetron.

Key Evidence

- When 5-HT₃ receptor antagonists are administered for more than 24 hours, the results of a meta-analysis indicate a small (4.1%) decrease in the absolute proportion of patients with delayed-onset emesis.
- A randomized trial showed no advantage when prolonged ondansetron administration was compared with metoclopramide 20 mg orally four times daily.
- No studies have compared the same 5-HT₃ receptor antagonist when given by the oral versus the intravenous route. Two studies of high-dose intravenous ondansetron versus oral granisetron suggest that the recommended dose of the latter is effective and may be regarded as equivalent to administration by the intravenous route.

UPDATE

- Two clinical practice guidelines (1u,2u), two meta-analyses (3u,4u), and four double-blind randomized controlled trials (5u-8u) were identified in the update search and were eligible for review.
- Two clinical practice guidelines from other practice guideline development groups produced recommendations which were consistent with the recommendations outlined above.
- A meta-analysis of 14 randomized trials (including seven non-blinded trials) did not detect statistically significant differences between granisetron and ondansetron for the prevention of acute or delayed nausea or vomiting for either moderately or highly emetogenic chemotherapy. Another meta-analysis, published in abstract form, with data from 28 randomized controlled trials detected no significant differences in acute or delayed nausea or vomiting between ondansetron, granisetron and tropisetron.

Treatment Alternatives

- Alternative approaches to delayed-onset emesis are the prolonged administration of dexamethasone 4 to 8 mg twice daily, or domperidone 20 mg orally four times daily.

XII. JOURNAL REFERENCE

Warr D, Bramwell V, Anderson D, Charette M, and the Systemic Treatment Disease Site Group. Use of 5-HT3 receptor antagonists in patient receiving moderately or highly emetogenic chemotherapy. *Curr Oncol* 2001;8:69-82.

XIII. ACKNOWLEDGMENTS

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For a full list of members of the Cancer Care Ontario Systemic Treatment Disease Site Group, please visit the Website of the Program in Evidence-based Care at <http://www.cancercare.ca/ccopgi>.

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UPDATE

This section includes all references from the review and updating activities.

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Appendix 1. Non-blinded randomized trials comparing 5-HT₃ receptor antagonists.

1st author (ref) year	# randomized (# evaluable)	Treatments	Conclusion
Bonnetterre (24) 1995	175 (150) cross-over	Ondansetron 8 mg IV then 8 mg t.i.d. X3 days Granisetron 3 mg IV	No significant difference in vomiting or nausea, or adverse events.
Gebbia (25) 1994	study 1: 182 (166) study 2: 164 (158)	Ondansetron 24 mg IV Granisetron 3 mg IV Ondansetron 16 mg IV Granisetron 3 mg IV	No significant difference in vomiting or nausea or adverse events.
Jantunen (26) 1993	166 (130) cross-over	Ondansetron 8 mg IV Granisetron 3 mg IV Tropisetron 5 mg IV	Granisetron superior to ondansetron for vomiting (p=0.034). Greater preference for granisetron (41.5%) than ondansetron (16.9%) (p-value not given). No significant difference in adverse effects.
Mantovani (27) 1996	117 (117)	Ondansetron 24 mg IV Granisetron 3 mg IV Tropisetron 5 mg IV	No significant difference in vomiting or nausea, or adverse events.
Martoni (28) 1996	124 (101) (cross-over)	Ondansetron 8 mg IV X3 on day 1 then 8 mg p.o. b.i.d. on day 2 Granisetron 3 mg IV on day 1	No significant difference in vomiting or nausea. Significant preference for granisetron (p=0.003) No significant difference in adverse effects.
Massidda (29) 1996	60 (60)	Ondansetron 8 mg IV Granisetron 3 mg IV Tropisetron 5 mg IV	No significant difference in vomiting. Ondansetron superior to granisetron and tropisetron for nausea (p<0.05).