Granisetron: An Update on its Clinical Use in the Management of Nausea and Vomiting

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Key Words. Granisetron · 5-HT3-receptor antagonist · Antiemetic · Nausea · Vomiting

ABSTRACT
Nausea and vomiting are typical side effects of cytotoxic therapy and some surgical procedures. These symptoms can represent a major therapeutic challenge and, if inadequately controlled by antiemetic treatment, will result in increased mortality, morbidity, and health care costs. However, the management of nausea and vomiting has improved greatly in recent years following the introduction of the 5-HT3-receptor antagonists, known as ‘setrons.’ In light of recent developments in antiemetic care, including the approval of the first neurokinin-1-receptor antagonist aprepitant (Emend®; Merck and Company, Inc.; West Point, PA) and a new 5-HT3 receptor antagonist palonosetron (Aloxi®; MGI Pharma; Minneapolis, MN), this article provides an update on the clinical experience gained with the 5-HT3-receptor antagonist granisetron (Kytril®; Roche Laboratories, Inc.; Nutley, NJ) for the management of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting, and also reviews its use in special patient populations. Granisetron is a potent and highly selective 5-HT3-receptor antagonist that has little or no affinity for other receptors, a characteristic that is thought to underlie the favorable side-effect and safety profiles of this agent. Extensive clinical trial data have shown granisetron to be an effective and well-tolerated agent for the treatment of nausea and vomiting in the oncology and surgical settings. Granisetron has also been shown to be effective and well tolerated in special populations, such as patients refractory to antiemetic treatment, patients with hepatic or renal impairment, and children. Data also suggest that its safety profile and minimal potential for drug-drug interactions would make it an antiemetic agent of choice for elderly cancer patients. The Oncologist 2004;9:673-686

INTRODUCTION
Nausea and vomiting can be clinically significant and severely debilitating side effects of cytotoxic chemotherapy, radiation therapy, and certain types of surgery. These symptoms can represent a major therapeutic challenge and, if inadequately controlled by antiemetic treatment, will limit a patient’s ability or desire to eat and drink, significantly reduce quality of life, threaten the success of therapy, and result in increased mortality, morbidity, and, importantly, health care costs [1-4].

The management of nausea and vomiting has improved greatly in recent years, with the introduction of 5-hydroxytryptamine3 (5-HT3, serotonin3)-receptor antagonists. These agents, also known as ‘setrons’ [5], are widely regarded as the most efficacious antiemetics available today and are currently recommended, in combination with corticosteroids, as the agents of first choice to control nausea and vomiting in most instances [6, 7]. Exciting recent developments in antiemetic therapies include the approval of the first neurokinin-1 (NK1) receptor antagonist for acute and delayed nausea and vomiting for use in combination with standard therapy regimens (a 5-HT3-receptor antagonist plus a steroid) and the approval of a new 5-HT3-receptor antagonist in the U.S. However, in contrast with the older agents, clinical trial data for these new agents are limited, and the effect of these drugs in ‘real world’ cancer patients remains largely unknown. In light of these developments in antiemetic care, a review of the current 5-HT3-receptor antagonists is appropriate, and the focus

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here is on the clinical use of granisetron (Kytril®; Roche Laboratories, Inc.; Nutley, NJ).

Granisetron is a potent and highly selective 5-HT3-receptor antagonist that has little or no affinity for other 5-HT receptors, or dopaminergic, adrenergic, benzodiazepine, histaminic, or opioid receptors [8]. In contrast, other 5-HT3-receptor antagonists have affinities for various receptor-binding sites. For example, ondansetron (Zofran®; GlaxoSmithKline; Research Triangle Park, NC) has detectable binding to 5-HT1B, 5-HT1C, α1-adrenergic, and µ-opioid receptor sites (Table 1) [9]. Although not proven, the binding of these agents to additional receptor subtypes other than their target receptor may underlie the inferior adverse-event profile seen with ondansetron compared with granisetron [10, 11].

This article provides an update on the clinical experience gained with granisetron to date in the management of chemotherapy-induced, radiotherapy-induced, and postoperative nausea and vomiting (CINV, RINV, and PONV, respectively) and reviews its use in special patient populations.

**Efficacy**

The efficacy of granisetron in the prevention of nausea and vomiting has been extensively studied in clinical trials, many of which use the stringent primary end point of total control, defined as no vomiting, no nausea, and no use of antiemetic rescue medication. The end point of complete control, defined as no vomiting, no worse than mild nausea and no use of rescue medication, is also extensively used. Most studies using granisetron have conformed with guidelines established for such studies, which, because of the somewhat subjective nature of nausea and even emesis, need a specific methodology [12].

**CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING**

**Acute Onset**

Early dose-comparison studies, using doses of 2-160 µg/kg, established that i.v. granisetron, 10-40 µg/kg, is effective in preventing acute nausea and vomiting (traditionally defined as occurring within the first 24 hours after administration of chemotherapy) in adult patients receiving moderately or highly emetogenic chemotherapeutic regimens (Table 2) [13-15]. No additional therapeutic benefit was obtained with doses >40 µg/kg. Overall, extensive data have been published demonstrating the efficacy of i.v. granisetron in clinical trials involving more than 6,000 patients, with the mean antiemetic complete response (i.e., no vomiting in the first 24 hours of chemotherapy) rate reported to be 66%, where the majority of trials reported used granisetron monotherapy [16].

The efficacy of oral granisetron, both 1 mg twice daily and 2 mg once daily, in patients undergoing moderately or highly emetogenic chemotherapy, has been demonstrated in numerous clinical studies (Table 3) [10, 17-28]. In addition,
<table>
<thead>
<tr>
<th>Granisetron schedule/chemotherapy emetogenicity</th>
<th>Study</th>
<th>Dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral twice daily/ moderate</td>
<td>Bleiberg et al. (1995) [17]</td>
<td>0.25, 0.5, 1, and 2 mg bid for 7 or 14 days</td>
<td>Maximum 24-hour complete response rate (no vomiting, no more than mild nausea, no use of other antiemetics, and no withdrawal) = 81.1% (1 mg dose)</td>
</tr>
<tr>
<td></td>
<td>Burris et al. (1996) [18]</td>
<td>Granisetron, 1 mg bid versus oral prochlorperazine, 10 mg bid, for 7 days</td>
<td>24-hour total control rate: granisetron = 58%; prochlorperazine = 33%; p &lt; 0.001</td>
</tr>
<tr>
<td>Oral twice daily/high</td>
<td>Heron et al. (1994) [19]</td>
<td>Granisetron, 1 mg bid for 7 days, versus granisetron, 1 mg bid for 7 days, + i.v. dexamethasone, 12 mg on day 1, versus i.v. metoclopramide, 3 mg/kg loading dose; 4 mg/kg infusion + i.v. dexamethasone, 12 mg on day 1, + oral metoclopramide, 10 mg 3 tds, for a further 6 days</td>
<td>24-hour total control rate (no nausea and no vomiting): granisetron = 43.7%; granisetron/dexamethasone = 54.7%</td>
</tr>
<tr>
<td>Oral 2 mg once daily/ moderate</td>
<td>Maisano et al. (1995) [20]</td>
<td>Granisetron, 2 mg once, versus granisetron, 1 mg twice</td>
<td>No vomiting or retching after 24 hours: 2 mg = 86.7%, 1 mg = 70%; no or mild nausea after 24 hours: 2 mg = 76.7%, 1 mg = 73.3%</td>
</tr>
<tr>
<td></td>
<td>Ettinger et al. (1996) [21]</td>
<td>Granisetron, 2 mg once, versus granisetron 1 mg twice</td>
<td>24-hour complete response rate (no nausea, no vomiting, no additional antiemetic medication): 2 mg once = 50.4%; 1 mg twice = 50.6%</td>
</tr>
<tr>
<td></td>
<td>Perez et al. (1998) [10]</td>
<td>Granisetron, 2 mg once, versus i.v. ondansetron, 32 mg</td>
<td>24-hour total control rate: granisetron = 59.4%; ondansetron = 58.0%, not significant</td>
</tr>
<tr>
<td>Oral 2 mg once daily/high</td>
<td>Gralla et al. (1998) [22]</td>
<td>Granisetron, 2 mg once versus i.v. ondansetron, 32 mg</td>
<td>24-hour total control rate: granisetron = 54.7%; ondansetron = 58.3%, not significant</td>
</tr>
<tr>
<td>Oral 2 mg/m moderate or high</td>
<td>Aapro et al. (2000) [23]</td>
<td>Granisetron, 2 mg once, + oral dexamethasone, 8 mg on day 1, followed by granisetron, 1 mg bid, + dexamethasone, 4 mg, versus metoclopramide, 20 mg + dexamethasone, 4 mg</td>
<td>Control of acute emesis: granisetron = 86%; metoclopramide = 85%</td>
</tr>
<tr>
<td>Oral 1 mg once daily/moderate</td>
<td>Martin et al. (1997) [24]</td>
<td>Granisetron, 1 mg once, + oral dexamethasone, 12 mg, versus i.v. ondansetron, 10 mg, + dexamethasone, 10 mg</td>
<td>Granisetron: nausea = 22%, vomiting = 10%; ondansetron: nausea = 27%, vomiting = 10%</td>
</tr>
<tr>
<td></td>
<td>Markman et al. (1998) [25]</td>
<td>Granisetron, 1 mg once, + i.v. dexamethasone, 20 mg</td>
<td>Patients who experienced any degree of nausea or vomiting during 24 hours following chemotherapy = 6%</td>
</tr>
<tr>
<td></td>
<td>Herrington et al. (2000) [26]</td>
<td>Granisetron, 1 mg once, + dexamethasone, 12 mg, versus oral ondansetron, 16 mg once, + dexamethasone, 12 mg</td>
<td>24-hour total control rate (not defined): granisetron = 46%; ondansetron = 45%; not significant</td>
</tr>
<tr>
<td></td>
<td>Hesketh et al. (2000) [27]</td>
<td>Granisetron, 1 mg once, versus granisetron, 2 mg once</td>
<td>24-hour total control rate: 1 mg = 54.2%; 2 mg = 57.1%</td>
</tr>
<tr>
<td></td>
<td>Lehoczky (1998) [28]</td>
<td>Granisetron, 1 mg once</td>
<td>24-hour complete response rate (no vomiting, no or mild nausea) = 83.4%</td>
</tr>
</tbody>
</table>

*Carboplatin-based chemotherapy.

Abbreviations: bid = twice daily; tds = three times daily.
the efficacy of a single 2-mg oral dose of granisetron has been shown to be as effective as two 1-mg doses given before and after chemotherapy, since the percentages of patients achieving total control were similar in both groups—50% in the 2-mg once-daily group and 51% in the 1-mg twice-daily group [21]. Furthermore, one trial indicated that a single dose of oral granisetron, 1 mg, may be as effective as a 2-mg once-daily dose in some patients receiving moderately emetogenic chemotherapy [27]. The equivalence of a single 2-mg dose of granisetron with i.v. ondansetron, 32 mg, has also been established in patients receiving both moderately emetogenic chemotherapy and high-dose cisplatin [10, 22].

More recent data suggest that the efficacy of granisetron (and ondansetron) in acute control of CINV can be enhanced by the addition of the newly approved NK1-receptor antagonist, aprepitant (Emend®; Merck and Company, Inc.; West Point, PA) [29-31]. In phase II trials, 80% of patients receiving granisetron plus the NK1-receptor antagonist were without emesis in the acute phase, versus 57% of those receiving granisetron alone (both groups also received dexamethasone [Decadron®; Merck and Company, Inc.]) [29].

Delayed Onset

The use of setrons to control delayed-onset emesis is established and accepted by recognized guidelines [32, 33]. Both i.v. and oral granisetron have been used in the control of delayed CINV, usually defined as occurring after 24 hours and up to 96 hours postchemotherapy [34-38]. For example, in a randomized study comparing granisetron, ondansetron, and tropisetron, i.v. granisetron, 3 mg, produced complete control of delayed vomiting (no vomiting or retching, days 2-5) in 73.7% of patients receiving moderately emetogenic chemotherapy, compared with 38.8% and 52.9% in ondansetron- and tropisetron-treated patients, respectively [38]. Granisetron was significantly superior to ondansetron in this regard (p = 0.014) and superior to both ondansetron and tropisetron in terms of major response rate (complete plus partial response rates) in the delayed phase (100% for granisetron versus 71.8% for ondansetron and 70.5% for tropisetron; p = 0.035 and 0.01, respectively). The authors of that study speculated that the higher control rate with granisetron may be due to its higher specificity and affinity for 5-HT3 receptors and its longer serum half-life than the other agents.

A further study comparing the efficacies of granisetron, ondansetron, and tropisetron in the control of delayed-onset nausea and vomiting in patients receiving moderate- or high-dose chemotherapy found similar efficacies among the three agents; complete response rates (no vomiting or retching) at 24-72 hours postchemotherapy were 55.5% in the granisetron-treated group, 48.5% in the ondansetron group, and 48.5% in the tropisetron group [39]. Despite the clear efficacy of the setrons in the prevention of nausea and vomiting in the acute phase, delayed-onset emesis remains unresolved in many patients.

However, recent trials have confirmed the efficacies of the setrons in the delayed phase, resulting in the approval of the new agent palonosetron (Aloxi®; MGI Pharma; Minneapolis, MN) for acute and delayed nausea and vomiting [40-42]. However, single-dose palonosetron has only been compared with single-dose ondansetron and single-dose dolasetron (Anzemet®; Aventis Pharmaceuticals Inc.; Bridgewater, NJ). First, ondansetron is recommended to be dosed as a single high dose or 2-3 times daily for full efficacy [43], and second, evidence suggests that the approved dose of dolasetron used in those trials may have been suboptimal [44-46]. Therefore, when compared with palonosetron, which also has a longer half-life than the other agents, it is not surprising that these trials demonstrate superior efficacy for palonosetron in the delayed phase. What is currently lacking are data comparing palonosetron with granisetron, an agent with a proven long duration of action [47] and efficacy as a once-daily medication. It is likely that, at equipotent doses, comparable efficacies would be demonstrated between these two agents in the acute phase and possibly in the delayed phase, and these trial data are awaited. In addition, antiemetic guidelines recommend the use of 5-HT3-receptor antagonists plus corticosteroids for highly and moderately emetogenic chemotherapy, as the addition of corticosteroids has been shown to enhance antiemetic efficacy. However, the palonosetron studies were conducted without concomitant corticosteroid use, and when corticosteroids were administered, they were done so at the discretion of the investigators. The benefits, if any, of palonosetron therapy in combination with corticosteroids in the ‘real world’ therefore remain unknown, particularly as corticosteroids help to ‘equalize’ the clinical efficacy of 5-HT3-receptor antagonists.

The development of the NK1-receptor antagonists also provides the opportunity for more patients to have good control of emesis in the delayed phase [48, 49]. Recent trials have indicated that the addition of aprepitant to standard dual-therapy regimens of ondansetron or granisetron plus dexamethasone improves the control of delayed CINV [29-31]. However, the efficacy of aprepitant alone in the delayed phase has not yet been compared with aprepitant plus 5-HT3-receptor antagonist given after day 1. (5-HT3-receptor antagonist combinations with aprepitant have currently been limited to day 1 of the study.) Indeed, it is uncertain at which point the predominantly serotonin-mediated emesis is replaced in time by a predominantly substance-P-mediated response, and patients may benefit from
additional 5-HT3-receptor antagonist administration after day 1 (i.e., on days 2 or 3). Studies to investigate the differential timing of serotonin-/substance-P-mediated emesis are warranted to determine the optimal therapeutic management of therapy-induced nausea and vomiting and to improve patients’ qualities of life.

**Radiotherapy-Induced Nausea and Vomiting**

Guidelines recommend the use of prophylactic 5-HT3-receptor antagonists in patients receiving highly or moderately emetogenic radiotherapy (e.g., total body irradiation, abdominal irradiation) on each day of therapy [6, 7, 33]. Sertrons are also recommended on an as-needed basis following low-emetogenic-risk procedures (e.g., radiation to the extremities or pelvis). Currently, only granisetron and ondansetron are indicated in most countries for the prevention and treatment of RINV.

Intravenous granisetron has been shown to be effective for the prevention of RINV in patients undergoing both total body irradiation [50-53] and lower hemibody irradiation [54]. In a double-blind, randomized trial involving 34 patients, oral granisetron (2 mg, 1 hour before the first daily fraction of radiation) and oral ondansetron (8 mg, 1 hour before each daily fraction) were shown to be more effective at preventing nausea and vomiting in patients receiving hyperfractionated total body irradiation (compared with an historical control group of 90 patients who received the same radiotherapy regimen but no 5-HT3-receptor antagonist) [55]. Although the trial did not involve a direct comparison of granisetron with ondansetron, some differences in efficacy were apparent. Over 60% of granisetron patients were without emesis versus 6.7% of patients in the control group; *p* < 0.01. Ondansetron was similarly superior to the control, but it was dosed three times daily and there was a lower proportion of patients in the ondansetron group without emesis (46.7%) than in the granisetron group (61.1%).

In the same study, the proportion of patients experiencing more than five emetic episodes over the 4-day study period was significantly less in the granisetron group (0%) than in the historic control group (55.6%; *p* < 0.01). In contrast, there was not a significant difference in this measure between the ondansetron treatment group and the control group (20% versus 55.6%; *p* = not significant).

**Postoperative Nausea and Vomiting**

Despite the fact that PONV occurs in about 10% of patients in the recovery room and 30% of patients during the first 24 hours after surgery [56], prophylaxis is only recommended for those at high risk or in whom vomiting may cause serious problems (e.g., head and neck surgery) [6]. Complete 24-hour control of nausea and vomiting may be particularly important in the outpatient surgical setting, as such patients may suffer symptoms subsequent to discharge. Problems of this nature may, therefore, lead to increased physician contact, emergency-room visits and, potentially, readmission to hospital, thus increasing health care costs. Indeed, a study conducted in the U.S. in 1994 calculated that the cost of managing PONV in the outpatient setting was $415 per patient [57].

A number of studies have shown the efficacy of both i.v. and oral granisetron in preventing PONV following different types of surgery, including major gynecologic surgery, thyroidectomy, laparoscopic cholecystectomy, fluorescein angiography, breast surgery, and pediatric surgery [58-66]. Granisetron is recommended at a dose of 1 mg i.v. for the prevention and treatment of PONV, though some studies have shown that granisetron at a dose of 0.1 mg is effective at preventing emesis [67].

**Safety**

It is important to consider the safety and tolerability of an agent when selecting antiemetic therapy in both the oncologic and postoperative settings. However, the side-effect profile of drugs used in cancer patients is particularly important, since such patients may be taking multiple medications or receiving treatment for comorbid conditions. This is particularly likely in the elderly, who comprise the majority of cancer patients [68]. The incidence of comorbidity increases with age [69], and polypharmacy is common among the elderly [70]. Many elderly patients also have decreasing organ function, and this population needs optimal supportive care measures that provide effective care while limiting unnecessary complications.

Furthermore, as cancer patients are likely to be suffering symptoms of their disease, they may be unable to tolerate any further reduction in their quality of life.

**Safety Profile**

The safety of i.v. and oral granisetron has been evaluated in more than 7,000 patients in clinical trials [16], which have shown the drug to be well tolerated, with mild and transient side effects. The most common adverse events occurring in clinical trials of i.v. granisetron were headache, asthenia, somnolence, diarrhea, and constipation (Table 4) [71]. There have been no reports of extrapyramidal side effects with either i.v. or oral granisetron for the prevention and treatment of chemotherapy-induced emesis [16].

The safety and tolerability of granisetron, in both i.v. and oral forms, have been compared with those of ondansetron in double-blind trials involving patients receiving moderately or highly emetogenic chemotherapy [72]. The frequencies and nature of adverse events were similar over the study period,
though significantly more patients receiving ondansetron experienced abnormal vision and dizziness (Table 5) [10, 11, 73]. The greater selectivity of granisetron than ondansetron for 5-HT3 receptors [9] may contribute to the lower incidences of these central nervous system side effects associated with granisetron in these studies.

The safety profile of i.v. granisetron was also shown to be similar to that of dolasetron in a double-blind trial involving highly emetogenic chemotherapy [74].

**Cardiac Toxicity**

Cardiovascular disease is a major cause of comorbidity and mortality in older patients with cancer [75]. It has been shown that 60% of patients aged 70 years or older have cardiovascular comorbidities [76]. Additionally, many cytotoxic agents, including anthracyclines and paclitaxel (Taxol®; Bristol-Myers Squibb; Princeton, NJ), can negatively affect cardiac function [77-79]. These factors should, therefore, be important considerations in the selection of antiemetic treatment.

A few reports have shown that some 5-HT3-receptor antagonists are associated with electrocardiographic (ECG) abnormalities [80]. However, the cardiac safety of granisetron has been demonstrated in studies involving both healthy volunteers and cancer patients [81-88]. In healthy adult volunteers, no clinically important cardiovascular changes (pulse rate, blood pressure, ECG, QTc interval) were observed with i.v. granisetron in doses up to 300 µg/kg [81, 82]. In addition, no significant cardiac arrhythmias were reported in a study investigating the effects of oral granisetron, 2 mg, in healthy adults after exercising in a hot environment [85]. Granisetron also has demonstrated cardiac safety when used at doses up to 160 µg/kg administered over 30 minutes in cancer patients; continuous monitoring for 24 hours after granisetron administration in patients receiving highly emetogenic chemotherapy revealed no clinically relevant changes in ECG, pulse rate, or blood pressure [87, 88]. Similarly, no clinically relevant cardiac changes (pulse rate, blood pressure, ECG, QRS duration, QTc interval) were observed with i.v. granisetron, 3 mg, in patients receiving chemotherapy, including doxorubicin (Doxil®; Alza Pharmaceuticals; Mountain View, CA; Rubex®; Bristol-Myers Squibb) and epirubicin (Ellence®; Pfizer; New York, NY) [83, 84]. Furthermore, rapid administration of granisetron, 3 mg, as a 1-second bolus injection to patients undergoing moderately to highly emetogenic chemotherapy did not affect QTc (end max), QTc (apex max), or QT-interval dispersion, and no cardiac events were associated with this agent [86].

**Drug-Drug Interactions**

Knowledge of the extent to which a particular drug interacts with enzymes of the hepatic cytochrome P450 (CYP) mono-oxygenase system is of vital importance, as such interactions may affect the clearance and bioavailability of coadministered drugs and could result in increased toxicities. This is particularly pertinent in cancer patients, given that combination therapy using a number of chemotherapeutic agents, often in conjunction with surgery or radiotherapy, has become increasingly common in the treatment of all forms of cancer in an effort to improve patients’ survival rates. Moreover, the issue of drug-drug interactions is particularly relevant in cancer patients given that they are likely to be receiving other prescribed drugs (e.g., antidepressants, cardiovascular agents) as well as over-the-counter, herbal, or alternative medicines [89]. A 5-year survey revealed that patients receive an average of 7.9 drugs during hospitalization [90], and that there is a higher risk of adverse drug reactions for patients receiving multiple drugs. Indeed, the theoretical risk of drug-drug interactions has been estimated to be >50% when a patient is

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**Table 4.** Most common adverse events in worldwide clinical trials of granisetron

<table>
<thead>
<tr>
<th>Incidence (% of patients)</th>
<th>i.v. granisetron (n = 3,269)</th>
<th>Comparator (n = 660)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

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**Table 5.** Percentage of patients experiencing adverse events following oral granisetron, 2 mg, or i.v. ondansetron, 32 mg, administration

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Granisetron</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>21.0</td>
<td>20.6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>16.2</td>
<td>18.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Dizziness (p = 0.011)</td>
<td>5.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Abnormal vision (p &lt; 0.001)</td>
<td>0.6</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Reprinted from Perez et al. (1998) [10] with permission from the American Society of Clinical Oncology.
receiving five medications, increasing to 100% when seven drugs are taken (Fig. 1) [91].

Although few studies have addressed the potential for drug interactions among 5-HT₃-receptor antagonists, chemotherapy agents, and drugs used in supportive care, many common drugs inhibit or are substrates/inducers of CYP isoenzymes and could, therefore, potentially interact with 5-HT₃-receptor antagonists [92-94] (Table 6). Granisetron is primarily metabolized by CYP3A enzymes and does not induce or inhibit any other CYP enzymes [95]. Conversely, other 5-HT₃-receptor antagonists also interact with other CYP enzymes. Ondansetron is metabolized primarily by CYP1A2, CYP2D6, and CYP3A4 [95, 96], while dolasetron and tropisetron are both metabolized by CYP2D6 as well as members of the CYP3A family (though this involvement is minor for tropisetron) [97, 98]. Palonosetron is also metabolized primarily through CYP2D6 with involvement of CYP3A4 and CYP1A2 [99]. Variation in activity of the CYP enzymes can affect the clearance and bioavailability of coadministered drugs, including antiemetics [100]. CYP2D6 is subject to genetic polymorphism that can lead to altered levels of enzyme activity, and this polymorphism varies by ethnicity [101-105]. 5-HT₃-receptor antagonists hepatically metabolized by CYP2D6 are subject to variable pharmacokinetics and efficacies as a result. Indeed, tropisetron serum concentrations [100] and area under the concentration-time curve (AUC) values [106] have been shown to correlate strongly with CYP2D6 activity. A higher serum concentration observed in patients who are phenotypically designated poor metabolizers (have slower drug clearance) [100, 106] may expose them to a higher risk for drug-drug interactions or a prolonged duration of adverse events. In addition, both tropisetron- and ondansetron-treated patients who are ultrarapid metabolizers (fast drug clearance) experience reduced drug efficacy and have been reported to experience significantly greater incidences of chemotherapy-induced vomiting than patients who are normal, poor, or intermediate metabolizers [100]. A similar, but nonsignificant, trend was observed for chemotherapy-induced nausea. In order to determine true risk, genetic testing would be required prior to administration of agents metabolized via CYP2D6. This is both costly and time consuming and it may, therefore, be appropriate to choose an agent that is not metabolized via this isoenzyme, such as granisetron.

![Figure 1. The probability of drug-drug interactions increases with polypharmacy. Adapted from Karas (1981) [91] with permission from The American College of Emergency Physicians.](http://theoncologist.alphamedpress.org/)

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology</strong></td>
<td>doxorubicin, lomustine</td>
<td>cyclophosphamide, doxorubicin, flutamide</td>
</tr>
<tr>
<td>5-fluorouracil, flutamide (Eulexin®; Schering-Plough Corporation; Kenilworth, NJ)</td>
<td>Bristol-Myers Squibb; Princeton, NJ)</td>
<td>flutamide</td>
</tr>
<tr>
<td><strong>Oncology supportive care</strong></td>
<td>ondansetron, ropivacaine</td>
<td>dolasetron, morphine, ondansetron, pethidine, tropisetron</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>propanol, verapamil, warfarin</td>
<td>flecainide (Tambocor®; 3M Pharmaceuticals; St. Paul, MN), propanolol, quinidine</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>cimetidine (Tagamet®; GlaxoSmithKline; Research Triangle Park, NC), omeprazole (Prolosec®; AstraZeneca; Wayne, PA)</td>
<td>cimetidine</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td>clo mipramine (Anafrani®; Mallinckrodt Inc.; St. Louis, MO), imipramine (Tofranil®; Mallinckrodt Inc.)</td>
<td>clo mipramine, imipramine, paroxetine (Paxil®; GlaxoSmithKline)</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td>phenobarbital, ropinirole (Requip®; GlaxoSmithKline)</td>
<td>selegiline (Eldepryl®; Watson Laboratories, Inc.; Corona, CA; Carbox®, Bristol-Myers Squibb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carbamazepine (Tegretol®; Novartis Pharmaceuticals Corp.; East Hanover, NJ; Carbalt®; Shire US Inc.; Florence, KY), phenobarbital</td>
</tr>
</tbody>
</table>

Table 6. Oncology, cardiovascular, gastrointestinal, and psychiatric agents that act as substrates/inhibitors/inducers of the cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4 [92-94]
While the possibility exists for granisetron to interact with chemotherapeutic agents and/or coprescribed drugs that affect CYP3A, to date, no drug interactions have been reported with granisetron [107]. In contrast, there are reports that ondansetron altered the systemic exposure of certain chemotherapeutic agents. In breast cancer patients receiving high-dose cyclophosphamide, cisplatin (Platinol®; Bristol-Myers Squibb), and carmustine (BiCNU®; Bristol-Myers Squibb) chemotherapy, treatment with ondansetron resulted in a significantly lower median AUC for cyclophosphamide than in control patients [108]. Also, ondansetron patients had significantly lower mean AUC values for both cyclophosphamide and cisplatin in cancer patients receiving the same chemotherapeutic agents, compared with patients in a prochlorperazine (Compazine®; GlaxoSmithKline) control group [107].

As with the introduction of any new therapeutic agent, caution must be exercised, and there are concerns of drug-drug interactions with aprepitant. Aprepitant is metabolized primarily via CYP3A4, with involvement from CYP2C19 and CYP1A2, and is a moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C9 [109]. To date, granisetron is the only antiemetic studied that does not interact with aprepitant, despite being metabolized primarily by CYP3A4. In contrast, coadministration of aprepitant has been shown to result in higher AUC values for ondansetron and dexamethasone, by 15% and 200%, respectively [110].

**Granisetron in Special Populations**

**Refractory Patients**

Lack of effective control during previous courses of chemotherapy predisposes patients to a higher incidence of nausea and vomiting than that seen in patients who have not previously experienced emesis during their treatment [111]. This is often related to a conditioned reflex, and anticipatory nausea and vomiting can be significantly reduced by the appropriate use of antiemetics from the beginning of chemotherapy [112].

Intravenous granisetron has been shown to be an effective antiemetic in patients who have not responded to other antiemetics, including ondansetron [113, 114]. For example, in a study of 517 cancer patients, 416 of whom had failed other antiemetics (including ondansetron, metoclopramide [Reglan®; Wyeth Pharmaceuticals; Collegeville, PA], and dexamethasone), i.v. granisetron, 3 mg, produced a complete response rate (no vomiting and, at worst, only mild nausea) of 53%–60% [114]. Moreover, in a double-blind, randomized study comparing 3 mg granisetron plus 10 mg dexamethasone with continued treatment with 8 mg ondansetron plus 10 mg dexamethasone in 40 patients receiving highly emetogenic chemotherapy, 47% of patients refractory to ondansetron in the first cycle obtained complete protection (no vomiting and no or mild nausea) with granisetron in subsequent cycles [115]. This latter study has, however, some methodologic problems and, while the results are interesting, the conclusions should not be regarded as evidence for lack of crossresistance among setrons. It may be that the efficacy of granisetron in patients refractory to ondansetron is due to its insurmountable binding properties, leading to once-daily dosing and 24-hour efficacy [116]. It may also be due to the fact that, in these refractory patients, ondansetron was not used as per the recommended prescription [43]. More recently, it has also been hypothesized that the response to granisetron in ondansetron-refractory patients may be because it is not metabolized via CYP2D6 and is, therefore, not subject to genetic polymorphism that may affect therapeutic efficacy [117].

A combination of i.v. granisetron plus prednisolone plus metopimazime is also a highly effective antiemetic treatment in patients receiving moderately emetogenic chemotherapy in whom granisetron or prednisolone plus metopimazime has failed [111]. The efficacy of granisetron in patients refractory to other antiemetics is further supported by a study showing that oral granisetron, 1 mg daily, is effective in preventing RINV in patients refractory to dopamine antagonists [118]. In that study one-third of patients experienced immediate remission of symptoms following the administration of granisetron, and all patients experienced remission of symptoms in 1-3 days.

There is also evidence to suggest that granisetron is effective in children refractory to standard antiemetics. In a study of 30 pediatric cancer patients (3-16 years) refractory to previous antiemetic treatment who received i.v. granisetron, 20 µg/kg, 77% of the patients had no nausea and minimal or no vomiting after treatment [119].

Patients failing after the use of setrons represent a special problem and there are no well-controlled studies in this setting to date [120].

**Hepatic and Renal Impairment**

Given that granisetron’s primary route of clearance from the body is via hepatic metabolism, it is important to know whether the clearance, efficacy, and safety of granisetron are affected in patients with malignant liver disease and hepatic dysfunction. These questions were addressed in a study comparing 20 patients with abnormal levels of liver enzymes and liver metastases with 19 cancer patients who did not have liver involvement, who received i.v. granisetron, 40 µg/kg, prior to highly emetogenic chemotherapy [119]. This analysis found no clinically significant differences in the efficacies and clearances of granisetron between groups. Furthermore,
Granisetron was well tolerated by both patient populations. Based on results of that study, dose adjustment of granisetron is not recommended in hepatically impaired patients [121]. Similarly, no dosage adjustment is recommended for renally impaired patients, as data show that the total clearance of granisetron is not affected in patients with severe renal failure who receive a single dose of i.v. granisetron, 40 µg/kg [121].

**Children**

Nausea and vomiting are just as debilitating in children as in adults, and there is evidence that granisetron is effective and well tolerated in this patient population. In a randomized, double-blind dose-ranging study involving 80 pediatric patients (mean age 10.3 years) scheduled to receive highly emetogenic chemotherapy, i.v. granisetron, 10, 20, or 40 µg/kg, was effective for over 24 hours at preventing nausea and vomiting. There were no significant differences in efficacies between doses, though a trend toward better control in the 40-µg/kg dose group was observed [119, 122]. Granisetron was well tolerated, and most symptoms were mild and transient.

The efficacy and tolerability of i.v. granisetron, 20 and 40 µg/kg, have also been shown in children with leukemia receiving high-dose methotrexate or cytarabine (DepoCyt®; Enzon, Inc.; Piscataway, NJ) [123], and with solid tumors receiving high-dose chemotherapy [124]. In a further study involving 40 patients aged 1-16 years with various types of cancer, i.v. granisetron, 40 µg/kg, produced an overall major and complete response rate (calculated based on the total score of a 5-point scale) of 82.5%, with the highest rate in younger children [125]. Intravenous granisetron, 20 µg/kg, has also been shown to be more effective than i.v. chlorpromazine (Thorazine®; GlaxoSmithKline), 0.3-0.5 mg/kg, plus i.v. dexamethasone, 2 mg/m², for the prevention of ifosfamide-induced (Ifex®; Bristol-Myers Squibb) emesis [126].

Many studies have documented the efficacy and safety of both i.v. and oral granisetron in the prevention of postoperative nausea in children. These mainly include the use of granisetron in children undergoing strabismus surgery or tonsillectomy [127-129].

**Ease of Administration**

Oral granisetron is administered as a 2-mg dose once daily (i.e., one dose provides efficacy over 24 hours). However, for patients in whom oral administration is not suitable, granisetron can also be administered intravenously via a 30-second injection or as a 5-minute infusion. The brief time required provides more convenience for patients and a better use of medical resources. Indeed, a crosscultural, multinational survey of oncology nurses highlighted the fact that nurses have insufficient time to perform many of their essential tasks and revealed that injections offered administration time benefits over infusions [130]. Furthermore, a 30-second injection of granisetron is well tolerated and is not associated with a higher incidence of local adverse events (e.g., injection site irritation) [11]. Additionally, a rapid, 1-second injection of granisetron is not associated with any adverse effects or cardiac abnormalities and may be an effective route of administration to save valuable nursing time [86]. Neither oral nor i.v. administration requires dose adjustment in patients with renal or hepatic impairment or in the elderly. Furthermore, clinical trials demonstrate that oral granisetron, 2 mg once daily, and i.v. granisetron, 30-second bolus i.v. injection, are equally effective and well tolerated in preventing CINV (Table 3) [11].

As a convenient, single, once-daily dose, granisetron has been shown to provide effective control of nausea and vomiting for a 24-hour period posttreatment in patients who have received either moderately or highly emetogenic chemotherapy. For example, 59% of patients who received moderately emetogenic chemotherapy achieved total control 24 hours after treatment with a single 2-mg dose of oral granisetron [131]. Likewise, once-daily granisetron, 2 mg, provided total control in 54.7% of patients who received highly emetogenic, cisplatin-based (Platinol®; Bristol-Myers Squibb) chemotherapy [22]. Furthermore, similar rates of total control (54.2%) have been achieved following administration of granisetron, 1 mg once daily, in patients receiving moderately emetogenic chemotherapy [27].

**Discussion**

The 5-HT₃-receptor antagonists, in combination with corticosteroids, have become the new standard of care for the prevention of nausea and vomiting with moderately to highly emetogenic chemotherapy [132]. These agents are also recommended for the prevention of RINV and are also used increasingly to control PONV [6]. Treatments used to control nausea and vomiting are part of the supportive care regimen and should not, therefore, add to patients’ side-effect burdens.

**Are all Agents the Same?**

Despite common perception that the 5-HT₃-receptor antagonists share equivalent efficacies and safety profiles, there are differences among the agents in terms of pharmacology, pharmacokinetics, and duration of action. There is evidence to suggest that there may also be differences in terms of efficacy in certain patient groups.

A recent meta-analysis compared the available 5-HT₃-receptor antagonists as prophylactic agents for acute chemotherapy-induced emesis following highly and
moderately emetogenic therapy [133]. A pooled analysis of cisplatin and noncisplatin studies showed an equivalence of ondansetron and granisetron, a significant advantage for granisetron over tropisetron, and no clear advantage of ondansetron over tropisetron. However, a subanalysis of i.v. granisetron, 3 mg, versus i.v. ondansetron, 8 mg, in noncisplatin-based studies indicated a possible advantage for granisetron [133]. While all 5-HT3-receptor antagonists may provide emesis protection following cisplatin, differences among antiemetic agents may become apparent with chemotherapies that have longer times to onset of symptoms (e.g., cyclophosphamide). In addition, another retrospective analysis carried out in the U.S. suggests that patients treated with ondansetron, 8 mg i.v., were not adequately protected from cyclophosphamide-induced emesis, when compared with those treated with ondansetron, 32 mg i.v., and granisetron, 1 mg and 10 µg/kg i.v. [134]. Furthermore, in a study by de Wit et al., demonstrating the efficacy of granisetron in ondansetron-refractory patients [115], patients may have initially experienced antiemetic failure following ondansetron therapy because it was administered as a single low dose (8 mg). Recent data also suggest differences in efficacy among palonosetron, ondansetron, and dolasetron [40-42].

CONCLUSIONS
Extensive clinical trial data have shown granisetron to be an effective and well-tolerated agent for the treatment of nausea and vomiting in the oncology, radiotherapy, and postoperative settings. It is also effective and well tolerated in special patient populations, such as patients refractory to antiemetic treatment, hepatically or renally impaired patients, and children.

Given the wealth of data in cancer patients and its low potential for drug-drug interactions and ease of administration, granisetron should be considered the antiemetic of choice in elderly cancer patients and in those at high risk for complications.

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