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REVIEW

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Granisetron: is there a dose–response effect on nausea and vomiting?

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Abstract *Purpose*: Nausea and vomiting are two of the most debilitating side effects of cytotoxic chemotherapy. Prevention of nausea and vomiting is, thus, very important to ensure that cancer patients continue to receive optimal cytotoxic therapy while seeking to maintain their quality of life. Significant advances in antiemetic therapy have been achieved since the introduction of the 5-HT_3 receptor antagonists, and these agents are currently regarded as first-line antiemetic agents. The aim of this article is to examine the hypothesis that there is a dose–response effect of granisetron for preventing chemotherapy-induced nausea and vomiting in cancer patients. *Methods*: A literature review of relevant publications was undertaken to provide a comprehensive review of issues related to the control of chemotherapy-induced emesis with escalating doses of granisetron. *Results*: There is evidence to suggest that there is a significant trend towards an improved efficacy of granisetron—in both the control of emesis and secondary end-points such as nausea and anorexia—with increasing doses, up to 40 μg/kg, in adults. At this dose, the likelihood of treatment success may be enhanced for most patients regardless of their individual emetogenic risk. Additionally, incremental doses of granisetron (up to 9 mg) have been shown to be effective and well tolerated in patients with refractory emesis. *Conclusions*: Those patients experiencing inadequate control of nausea and vomiting following granisetron may also benefit from retreatment with supplementary doses of granisetron, and over subsequent chemotherapy cycles, these patients should receive granisetron 40 μg/kg to ensure emesis protection.

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Introduction

Nausea and vomiting are significant and debilitating side effects of cytotoxic chemotherapy and radiation therapy bringing considerable discomfort to the lives of cancer patients, potentially lasting for more than 5 days following therapy. Prevention of nausea and vomiting is thus very important, the goal being to enable each patient to resume and continue their daily routine immediately after chemotherapy or radiotherapy.

The symptoms of nausea and vomiting impact on all aspects of patients' lives [29], and are consistently rated by patients as two of the most severe side effects of chemotherapy [34, 52]. Significantly, however, following the introduction of 5-HT_3 receptor antagonist antiemetics, vomiting is now no longer ranked by patients as the most severe side effect; they now consider nausea to be the most debilitating consequence of curative therapy [34, 52].

Nausea and vomiting associated with chemotherapy can be classified as acute, delayed or anticipatory [9, 75]. Acute nausea and vomiting occurs within the first 24 h of treatment with chemotherapeutic agents and delayed emesis occurs more than 24 h after chemotherapy and can last for more than 5 days [75]. Anticipatory nausea and vomiting can occur prior to chemotherapy or radiotherapy and is often a consequence of poorly controlled nausea and vomiting in previous treatment cycles.

Prophylactic use of antiemetics to control nausea and vomiting is standard practice in patients receiving moderately to highly emetogenic chemotherapy [50]. 5-HT_3 receptor antagonists like granisetron are now considered the 'gold standard' in antiemetic therapy [28]. Prophylactic antiemetic therapy must never be compromised, and the importance of total control of emesis—that is, no nausea, no vomiting and no rescue medication—in the first cycle of chemotherapy correlates with the frequency

and occurrence of delayed and anticipatory nausea and vomiting in patients [30, 35, 38, 51, 55, 65, 75]. Indeed, all published guidelines clearly state that the goal of antiemetic care is to *prevent* nausea and vomiting. Therefore, good control of nausea and vomiting with 5-HT_3 receptor antagonists, in which the patient can resume a normal routine with minimal disruption, may necessitate increasing the dose of antiemetic in individuals who do not respond adequately to treatment.

The pharmacology of emesis and the 5-HT_3 receptor antagonist granisetron are reviewed in this paper focusing on the issue of the dose–response effect of granisetron, considering the consequence that lower-than-optimal doses may have on treatment outcome, patient quality of life and patient compliance. Clinical studies consistently show a trend towards increased efficacy of antiemesis with increasing doses of granisetron [16, 54, 59, 72, 73, 81, 89]. Although many patients respond well to the recommended dose of granisetron, data demonstrate that patients experiencing unsatisfactory control of nausea and vomiting with granisetron can respond to supplementary doses and doses of granisetron that are higher than generally used [89]. In addition, patients refractory to other 5-HT_3 receptor antagonists respond well to granisetron, sometimes at doses that may be higher than generally used, in subsequent chemotherapy cycles [28, 36, 90].

Clinical pharmacology

The emetic response

Emesis induced by cytotoxic agents is mediated by events culminating in the release of 5-HT from enterochromaffin cells in the gastrointestinal mucosa [70]. Thereafter, 5-HT stimulates 5-HT_3 receptors located on abdominal vagal afferent neurones which terminate directly beneath the area postrema in the nucleus tractus solitarius, thereby eliciting the vomiting reflex [63]. The area postrema, a circumventricular organ, is considered to be one of the 'windows of the brain' outside the blood–brain barrier, and is ideally situated to detect circulating noxious substances to elicit the vomiting reflex and expel accidentally ingested or accumulating toxins. This vomiting reflex initiated by the stimulation of the vagal afferent neurons and/or stimulation of the area postrema is not exclusive in eliciting vomiting. Vomiting can occur even when vagal afferents have been severed, possibly resulting from direct stimulation of the gut mucosa [4].

The 5-HT_3 receptor antagonists

The 5-HT_3 receptor antagonists differ considerably in their biological properties such as receptor specificity, potency and plasma half-life [5, 21, 55, 79]. Granisetron is highly specific for 5-HT_3 receptors, having little or no affinity for other types of serotonergic receptors or dopaminergic, adrenergic, benzodiazepine, histaminic, picrotoxin or opioid receptors [18, 21]. This is in contrast with ondansetron which, despite having a high affinity for the 5-HT_3 receptor, also shows appreciable affinity for 5-HT_{1B}, 5-HT_{1C}, α_1-adrenergic and μ-opioid receptors [97].

In contrast to ondansetron, which acts by stimulation of 5-HT_3 receptors on abdominal vagal nerves, granisetron acts on both 5-HT_3 autoreceptors on enterochromaffin cells [48] and on vagal afferents [18, 19]. Examination of the binding of 5-HT_3 antagonists to rat vagal 5-HT_3 receptors reveals that granisetron and tropisetron display insurmountable antagonism at 5-HT_3 receptors and cannot be displaced by the addition of further 5-HT, while ondansetron exhibits competitive antagonism at these receptors [76]. While data for receptor binding of granisetron, ondansetron and tropisetron to 5-HT_3 receptors are forthcoming, the binding of dolasetron has not been completely characterized. The nature of this antagonism by granisetron is thought to underlie the fact that its pharmacodynamic half-life far exceeds its plasma half-life—in patients, the plasma half-life of granisetron is reported to be around 10 h [60], whereas the efficacy of the once-daily dosing regimen of granisetron would indicate that the duration of receptor blockade is at least 24 h [26]. Data accumulated from 5-HT-mediated cutaneous flare response experiments corroborate the long in vivo duration of granisetron. Granisetron 40 μg/kg significantly reduces the axon-reflex flare for up to 24 h following a single intravenous infusion [31, 94]. This long duration of action is in contrast to that of ondansetron, which has a short plasma half-life [100] and displays competitive antagonism at 5-HT_3 receptors [76], thus necessitating multiple daily dosing [100].

No clinically significant drug interactions involving granisetron have been documented to date—the potential for drug interactions with granisetron is low because it is only metabolized by the hepatic enzyme subfamily cytochrome P450 (CYP) 3A and does not induce or inhibit any other cytochrome enzyme [17, 20]. This contrasts with dolasetron which is metabolized by CYP2D6 and CYP3A4 enzymes [20, 85], and ondansetron which is metabolized by the enzymes CYP1A1, CYP1A2, CYP2D6 and CYP3A4 [20, 37]. The clearance of granisetron is not altered in hepatically impaired patients and, despite having a 50% reduction in total clearance compared with normal patients [77], it is unlikely that this difference translates into a clinical effect.

Overall, the insurmountable antagonism and high affinity of granisetron for 5-HT_3 receptors is thought to be responsible for its good clinical efficacy, and its high receptor selectivity combined with the low risk of drug interaction for its minor side-effect profile.

Allosteric modulation

The 5-HT_3 receptor belongs to the ligand-gated ion channel superfamily, and it is clear that this receptor

complex possesses pharmacologically distinct recognition sites by which the receptor can be allosterically modulated [23, 78]—allosteric modulators bind to a site on the receptor that is different to the binding site of the natural agonist. Among agents that can modulate the receptor complex are protein kinase inhibitors [56], 5-hydroxyindole [96], anaesthetic agents and alcohols [13, 78].

Of significant relevance to an individual cancer patient's susceptibility to emesis following chemotherapy is the modulation of the 5-HT_3-receptor complex by alcohol. Extracellular electrophysiological recording of isolated rat vagus nerves reveals the ability of 2,2,2-trichloroethanol and related alcohols at millimolar concentrations to increase the magnitude of 5-HT_3-mediated depolarization [13]; it has been known for some time that nausea and vomiting following chemotherapy or radiotherapy is affected by the patient's history of alcohol intake [38]. The 5-HT_3-receptor complex displays homologous topological organization to the nicotinic acetylcholine receptor [40] and as such can be activated by nicotinic ligands. Nicotine, therefore, may also have the ability to modulate the 5-HT_3 receptor; yet another factor to take into consideration when assessing patient susceptibility to emesis.

This allosteric modulation of the 5-HT_3 receptor may result in huge potential variation in patient vulnerability to developing nausea and vomiting as a result of chemotherapy, radiotherapy or surgery. Thus, some patients might require higher than recommended doses of the 5-HT_3 receptor antagonist antiemetic agents to compensate for the change in receptor complex.

Dose-ranging studies

Preclinical

Clinical investigation into the safety and effectiveness of 5-HT_3-receptor antagonists has been greatly facilitated by the study of antiemetic therapies in animals treated with cytostatic agents. Ferrets exhibit an emetic response to the same range of emetic stimuli as that seen in humans [6] and have since become the animal model of choice in investigating emesis.

Studies on both ferrets [41] and mice [93] have confirmed that the 5-HT release and the serotonergic contraction of isolated ileum is mediated by the 5-HT_3 receptor, thereby substantiating the theory that 5-HT_3 receptor blockade in the gut mediates part of the antiemetic response. These valuable in vitro experiments have identified granisetron (0.3–1 n*M*), tropisetron (1–10 n*M*) and ondansetron (10 nM to 1 μ*M*) as being able to dose-dependently inhibit 5-HT-induced contractions [93]. Furthermore, granisetron can dose-dependently decrease the amplitude of electrically evoked contractions in the guinea pig isolated ileum [15].

Examination of the 5-HT_3-receptor antagonists as antiemetic agents in ferrets identifies apparent differences

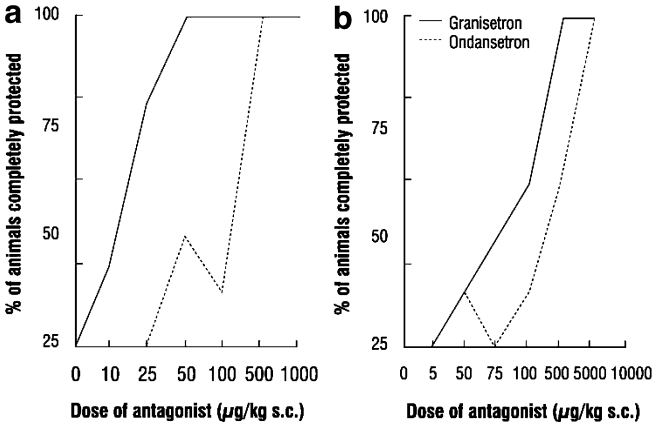

Fig. 1a, b Comparison of the efficacy of granisetron vs ondansetron administered subcutaneously (s.c.) in protecting ferrets from emesis following (**a**) total body irradiation (200 rad, 250 kV) or (**b**) cisplatin (10 mg/kg i.v.). Results are expressed as the percentage of animals in the group experiencing no retches or vomits (complete protection). Group size $n = 4–6$ at each dose. Reprinted from reference 7, with permission from Elsevier Science

in the dose–response profile of each agent [18]. The antagonists characteristically display either curvilinear (e.g. granisetron) or non-linear monotonic (e.g. ondansetron) dose–response profiles (Fig. 1) [7]. The profile of granisetron as an antiemetic agent has been examined in numerous studies in ferrets exposed to either X-irradiation or high-dose cisplatin [4, 7, 14, 15, 66, 71] making direct comparisons with ondansetron [4, 7] or azasetron [15]. Such studies have demonstrated that the number of emetic episodes—as well as secondary behaviours such as the number of burrowing and backing episodes, described as peri-vomiting behaviour—induced by either X-irradiation or cisplatin, decrease in a dose-dependent manner with increasing doses of granisetron (0.005–5 mg/kg) (Fig. 2) [4]. Ondansetron and azasetron, on the other hand, are less effective at high doses, with an observed decrease in antiemetic efficacy. Similarly, following the administration of tropisetron to cancer patients undergoing moderately or highly emetogenic chemotherapy, tropisetron 5 mg i.v. was more effective (not significant) at preventing emesis than 10, 20 or 40 mg i.v., with no additional antiemetic benefits observed following administration of higher doses (Fig. 3) [46]. This is in contrast to evidence from preclinical studies that have suggested a linear dose–response profile [18].

In addition to the marked difference in dose–response profile, granisetron is five- to tenfold more potent than ondansetron at completely protecting animals from X-irradiation- or cisplatin-induced emesis [4, 7]. This is reflected in clinical practice, where the dose of granisetron administered to patients is much lower than that of ondansetron [60, 100]. Similarly, the duration of antiemetic action of granisetron in ferrets is twice that of ondansetron, which is again reflected in clinical practice by the efficacy of once-daily dosing of granisetron compared with multiple dosing with ondansetron [26].

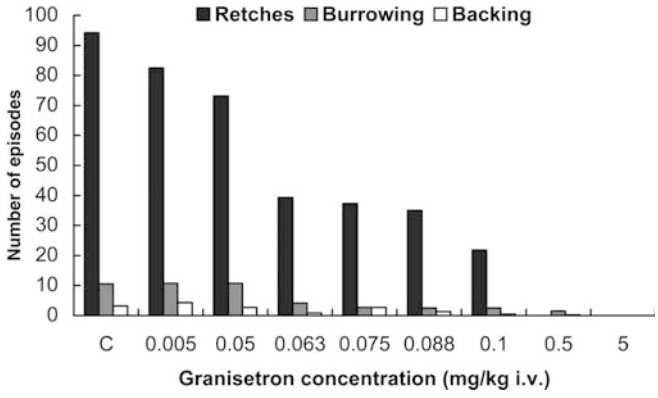

Fig. 2 The dose-dependent effect of granisetron (0.005–5 mg/kg i.v.) against retching and peri-vomiting behaviour induced by cisplatin (10 mg/kg i.v.) in the ferret (*C* control). Data from reference 4

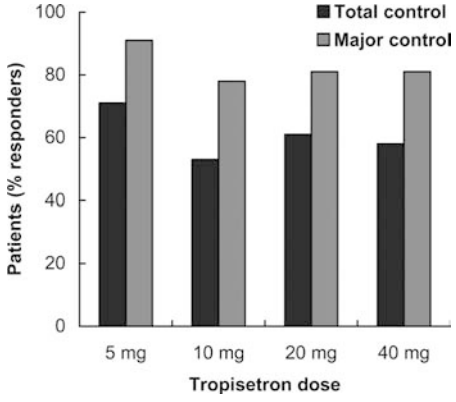

Fig. 3 Non-linear dose–response profile of tropisetron in patients receiving moderately or highly emetogenic chemotherapy (cisplatin > 50 mg/m^2). *Total control* no vomiting, *major control* no more than two vomits; 5-mg group $n = 35$; 10, 20 and 40-mg groups $n = 36$. Data from reference 46

Clinical

In general, the preclinical studies described above are reflected in the clinical data. Classically, granisetron is regarded as having only a modest dose–response curve within a small dose range, with a threshold effect for response and a plateau in therapeutic efficacy extending over a severalfold range in dose [47]. However, closer inspection of the clinical data with regard to dose and antiemetic efficacy, and secondary end-points such as nausea and anorexia, enables a different picture to emerge.

Intravenous granisetron doses between 10 and 160 μg/kg [45, 59, 72, 73, 81, 88, 89] and 1 and 3 mg [67], and oral doses of 1–2 mg [16, 54], are effective for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea and vomiting (RINV) and postoperative nausea and vomiting (PONV). The lowest effective dose of granisetron currently recommended by antiemetic guidelines is

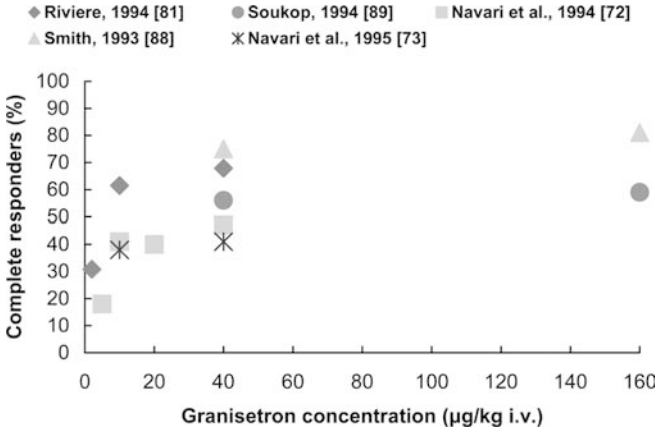

Fig. 4 The dose-dependent effect of granisetron (2–160 μg/kg i.v.) in cancer patients undergoing moderately or highly emetogenic chemotherapy regimens. Efficacy is measured by the proportion of complete responders (no vomiting and no use of rescue medication) in the treatment population (■ reference 72, ∗ reference 73, ♦ reference 81, ▲ reference 88, ● reference 89)

10 μg/kg [51]. However, the lowest effective dose does not necessarily translate into the optimum dose, and European doses are three times higher than those approved in the USA.

A number of clinical studies support the preclinical pharmacological data for granisetron in indicating that there is a trend of increasing efficacy of granisetron with ascending intravenous doses (Fig. 4) [59, 72, 73, 81, 88, 89]. Granisetron 40 μg/kg is reported to be consistently more effective than 2 and 10 μg/kg [59, 81] and than 5, 10 or 20 μg/kg [72]. Although the difference between the highest and the intermediate doses does not reach statistical significance, there is a trend in the number of patients experiencing a complete response (no vomiting and no use of rescue therapy; $P = 0.011$) and major response (no more than two vomiting episodes, including complete responders; $P = 0.002$) [72]. Even in those studies in which only two high doses of granisetron (40 and 160 μg/kg) have been examined, there was increased efficacy with the higher dose [88, 89]: at the end of 24 h, 75% of patients in the granisetron 40 μg/kg treatment group and 81% in the granisetron 160 μg/kg group were complete responders (no vomiting and no or only mild nausea) [88].

Paediatric patients are a good example of where the *lowest* effective dose does not necessarily translate into the *most* effective dose. In children receiving granisetron as prophylaxis for PONV, 50% fewer experienced vomiting episodes at a dose of 80 μg/kg than at a dose of 40 μg/kg [45]. Both the 40 μg/kg and the 80 μg/kg granisetron doses resulted in significant improvement of PONV compared with placebo, but there was no significant difference in the results between patients receiving 40 μg/kg and those receiving 80 μg/kg due to limited patient numbers. Consequently, 40 μg/kg was recommended as the effective dose since it was significantly more effective than 20 μg/kg ($P < 0.05$). Nonetheless, the data favoured the higher doses: 65% of

Table 1 Paediatric patients showing complete control of emesis (no vomiting episodes[a]) with granisetron 10–80 μg/kg

Reference	Indication	Granisetron dose (μg/kg)			
		10	20	40	80
45	PONV	–	40%	80%	85%
62	CINV	25%	50%	69%	–
61	CINV	21%	31%	32%	–
92	CINV	–	38%	74%	–

[a]Children cannot properly express their subjective feelings of nausea and therefore complete control of emesis is often evaluated primarily based on the frequency of vomiting

Table 2 Efficacy of granisetron by dose and secondary end-point during 24 h following high-dose cisplatin chemotherapy. Adapted with permission from reference 72

	Granisetron dose (μg/kg)				P^a
	5 ($n=40$)	10 ($n=49$)	20 ($n=48$)	40 ($n=47$)	
Nausea free	15	35	38	43	0.009
Without anorexia[b]	40	51	56	62	0.040

[a]Linear trend
[b]Patients who were able to eat and drink at some time during the 24-h study period

placebo-treated patients experienced postoperative retching and vomiting compared with 60%, 20% and 15% of patients treated with granisetron at 20, 40 and 80 μg/kg, respectively [45]. A further three studies have demonstrated increased effectiveness of antiemetic treatment with increasing doses of granisetron up to 40 μg/kg (Table 1) [61, 62, 92].

Secondary end-points

Examination of secondary end-points, such as nausea and anorexia, which can be just as disabling to an individual as vomiting, reveal a tendency towards granisetron 40 μg/kg producing the most favourable response. There is a significant linear trend supporting high doses for patients free of nausea ($P=0.001$) and without anorexia ($P=0.04$) after administration of granisetron as prophylaxis for highly emetogenic cisplatin chemotherapy (5–40 μg/kg) (Table 2) [72]. Consistent with this observation are the results of Riviere [81] who reported that the percentage of patients nausea- and emesis-free increased linearly through increasing doses of granisetron: 44.2%, 59.6% and 66.0% of patients were nausea-free following 2, 10 and 40 μg/kg granisetron, respectively, with 38.5%, 65.4% and 73.6% of patients being emesis free. Furthermore, in another study, whereas total control rates (defined as no nausea, no vomiting and no use of rescue antiemetics) in patients following high-dose cisplatin were 28% and 33% for granisetron 10 and 40 μg/kg, respectively, an even greater difference in the effectiveness of the doses was apparent in terms of the frequency of nausea experienced by these patients [73]: 28% of patients receiving granisetron 10 μg/kg experienced no nausea during the 24-h period following chemotherapy, while 36% of patients were symptom-free following granisetron 40 μg/kg [73].

Supplementary doses and refractory patients

In addition to a trend of increased efficacy with increasing doses of granisetron, patients with poorly controlled emesis have been shown to respond to supplementary doses of granisetron. Not only that, but higher initial doses of granisetron as prophylaxis for CINV result in fewer patients requiring additional 'rescue' therapy. It has been observed that over half (57.7%) of patients receiving granisetron 2 μg/kg i.v. require at least one additional dose of granisetron, whilst 36.5% of those treated with granisetron 10 μg/kg, and only 28.3% of those receiving granisetron 40 μg/kg, need rescue therapy [81]. In two further studies, patients undergoing highly [89] or moderately [88] emetogenic chemotherapy treated with granisetron 40 or 160 μg/kg i.v. as prophylaxis for CINV were offered up to two additional doses to treat emergent symptoms of nausea and vomiting, after which stage, if symptoms were still uncontrolled, patients could be treated with standard antiemetics. Supplementary doses of granisetron at 40 and 160 μg/kg were effective within minutes, providing relief in 87–92% and 84–90% of patients, respectively [88, 89]. Furthermore, twice as many patients treated with granisetron 40 μg/kg required conventional antiemetic therapy (6%) compared with patients who received granisetron 160 μg/kg (3%) [88].

A subset of patients refractory to treatment with ondansetron have been shown to benefit from granisetron [28, 36, 90]. A single dose of granisetron 3 mg i.v. is an effective antiemetic regimen in these patients. However, Carmichael et al. have reported that some patients (20%) require supplementary doses of granisetron [28]. These studies demonstrate that, even if patients have inadequate control of nausea and vomiting during therapy with emetogenic agents, after administration of one 5-HT_3 receptor antagonist (e.g. ondansetron), they are able to respond well to another 5-HT_3 receptor antagonist (granisetron). This has been postulated to be related to the superior selectivity and longer duration of receptor blockade with granisetron compared with ondansetron [22].

Subtherapeutic dosing

It is increasingly common practice to administer the 5-HT_3 receptor antagonists at doses that are below those recommended by the drug manufacturer in an attempt to lower the overall cost of antiemetic therapy. The efficacy of ondansetron is most effective when administered as multiple doses over 24 h (0.15 mg/kg i.v. three times daily) or as a single high dose (32 mg i.v.); however, it is frequently used as a single low dose (8 mg once

daily), thus compromising the control of emesis in individual patients [12, 24, 57, 86, 91], particularly those receiving chemotherapy with agents producing nausea and vomiting during the late-acute period (e.g. cyclophosphamide [39]). Data also suggest that even the recommended doses of oral dolasetron (100 mg) [25, 53, 63] and intravenous tropisetron (5 mg) [64, 68, 95] are subtherapeutic. In turn, subtherapeutic dosing and incomplete control of nausea and vomiting often result in additional antiemetic dosing and lessened patient quality of life. This is in contrast to granisetron, where 1 mg has also been shown to be effective at preventing both nausea and emesis in cancer patients undergoing moderately or highly emetogenic chemotherapy [16, 54, 59, 72, 73, 81, 84, 88, 89]. However, the dose–response benefit for granisetron supports 3 mg as the optimal antiemetic dose for cancer patients.

Safety considerations

Granisetron is well tolerated at all doses tested and there are no significant differences in adverse events across the dose-range of granisetron [2, 3, 59, 72, 73, 81, 88, 94]. Doses of granisetron up to 300 μg/kg i.v. are well tolerated in healthy volunteers [3, 94] and 240 μg/kg i.v. in patients undergoing chemotherapy [89]. This is most probably attributable to the high affinity and selectivity of granisetron for the 5-HT_3 receptor. In children, granisetron is also well tolerated, with no significant difference in adverse events with doses of 80 and 100 μg/kg [44, 45]. The most frequently experienced adverse events are headache and constipation, although comparatively there is a lower risk of severe headache, dizziness and blurred vision with granisetron than with ondansetron [49]. Indeed, in a trial with 1085 cancer patients receiving moderately emetogenic chemotherapy, only 5.4% and 0.6% of patients experienced dizziness or blurred vision following administration of granisetron 2 mg orally compared with 9.6% ($P = 0.011$) and 4.2% ($P < 0.001$) of those receiving ondansetron 32 mg i.v., respectively [80].

Cardiovascular disease is a major cause of comorbidity and mortality in older patients with cancer [98], and many cytotoxic agents can negatively affect cardiac function [33, 42, 83]. Cardiovascular parameters are unaffected by bolus or a slow-infusion of i.v. granisetron, with only a slight (though significant) decrease in diastolic blood pressure in some patients [27] and healthy volunteers [94] with doses up to 160 μg/kg (i.e. fourfold higher than the standard 40 μg/kg dose). This is in contrast to both tropisetron and dolasetron, which have been reported to cause QTc prolongation, and consequently carry a cardiovascular precaution or warning in their respective prescribing information [8, 74]. Ondansetron also reportedly affects ECG parameters in cancer patients [11, 49], although these do not necessitate precautions or warnings in its prescribing information. There is currently a lack of data regarding cardiovascular effects in cancer patients following the use of ramosetron.

Drug–drug interactions

Estimates suggest that during an average hospital stay, patients may receive up to ten different medications, and the use of concomitant medication may increase a patient's risk of drug–drug interactions [20]. The elderly may be particularly at risk of such interactions since they have more comorbidities, and an increased use of concomitant medication has been reported in patients over the age of 65 years [32, 43, 99].

The 5-HT_3 receptor antagonists are metabolized by the hepatic CYP enzymes. Hepatic metabolism of granisetron is via the CYP3A isozymes [17, 20]. Ondansetron, dolasetron and tropisetron are also all metabolized by CYP3A isozymes; however, each is also metabolized by CYP2D6, and the metabolism of ondansetron also involves CYP1A2 and CYP1A1 enzymes [20]. Genetic polymorphism of CYP2D6 [58], declining organ function during aging [10, 69], in addition to increased comorbidities and polypharmacy in the elderly, all create an increased risk for drug–drug interactions in cancer patients that may affect the efficacy or safety of supportive care agents such as the 5-HT_3 receptor antagonists.

The metabolism of granisetron by a single family of CYP isozymes decreases its potential risk of drug–drug interactions and, unlike other agents, granisetron has not been reported to inhibit or induce hepatic metabolism [20]. In addition, it is not metabolized by the hepatic pathway linked to genetic polymorphism or ethnic variation, making it a good first choice antiemetic agent. There have been no reports of adverse drug interactions following the administration of incremental doses of granisetron.

Discussion

Individual patient susceptibility to cytostatic agent-induced nausea and vomiting varies considerably; emetogenicity of therapy, patient characteristics such as age and gender, concomitant therapies and prior exposure to chemotherapy regimens all influence individuals' propensity to nausea and vomiting [38, 82]. Thus, some patients will require higher doses of 5-HT_3 receptor antagonist antiemetic agents. In support of this, Carmichael et al. have proposed that on an individual basis there is no apparent threshold level of plasma granisetron for effect [26], indicating that the likelihood for antiemetic success may vary from patient to patient. With this in mind, it may be inappropriate to set a limit on the dose of antiemetic agent administered, but rather leave it open to interpretation by the consulting physician. It is the physician's

responsibility to report an adequate history of the patient, taking into consideration all predisposing factors for nausea and vomiting. Only then should a decision be made as to the correct dose of antiemetic agent required by each patient. Considering the goal of *preventing* nausea and vomiting, the physician's decisions need to reflect which dose will consistently avert emesis in each patient. The probability of success will be maximized by the choice of the initial loading dose. Thus, maximum prevention of nausea and vomiting may result following administration of granisetron 40 μg/kg i.v. The dose–response profile of granisetron means that incremental increases in dose will lead to improved antiemetic success; more patients should experience total control of nausea and vomiting with higher doses. In contrast, neither ondansetron nor tropisetron exhibit classic dose–response curves, and in the case of ondansetron, mid-range doses have been shown to result in reduced antiemetic efficacy.

The majority of clinical data have been accumulated from the antiemetic efficacy observed following first-cycle chemotherapy. However, studies that incorporate successive chemotherapy cycles have revealed a tendency towards patient resistance to antiemetic therapy with subsequent cycles [35, 87]—a cycle-to-cycle effect. This loss of complete control of emesis over subsequent cycles is often interpreted as being due to a patient's previous experience of emesis control. Although the psychological perceptions of patients should never be underestimated, loss of complete control may also be partly due to the characteristics of the 5-HT_3 receptor. Under these circumstances, a higher concentration of 5-HT_3 receptor antagonist may well be required to produce the same magnitude of response.

Nausea and vomiting should be prevented since these symptoms have a serious and debilitating affect on patients following radiotherapy, chemotherapy and surgery, and may compromise patient compliance with subsequent treatment cycles, as well as adversely affect treatment outcome. As described in this review, there is a trend towards an improved efficacy of granisetron—in both the control of emesis and secondary end-points such as nausea and anorexia—with increasing dose up to 40 μg/kg in adults. At this dose, the likelihood of treatment success may be enhanced. Moreover, those patients experiencing inadequate control of nausea and vomiting following treatment with granisetron, can benefit from retreatment with supplementary doses of granisetron. Over subsequent chemotherapy cycles, these patients should receive granisetron 40 μg/kg to ensure emesis protection. Furthermore, in support of increasing dose benefits, this review also highlights the good tolerability profile of high-dose granisetron in both adults and children, further enhancing the likelihood of antiemetic therapy success.

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