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REVIEW ARTICLE

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Granisetron in the control of radiotherapy-induced nausea and vomiting: a comparison with other antiemetic therapies

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Abstract Radiotherapy-induced nausea and vomiting (RINV) can be one of the most distressing symptoms of radiotherapy treatment, which if incompletely controlled may last for several weeks with fractionated radiotherapy and prevent completion of the planned treatment course. Current treatment guidelines recommend the use of 5-HT_3 receptor antagonists with or without corticosteroids for highly and moderately emetogenic radiotherapy, though only granisetron and ondansetron are currently indicated for RINV in most countries. Granisetron is a potent and highly selective 5-HT_3 receptor antagonist, with demonstrated efficacy in RINV in both placebo-controlled and comparative studies. In this paper the clinical experience with granisetron in RINV is reviewed, and its efficacy and safety compared with other antiemetic therapies.

Keywords Nausea and vomiting · Radiotherapy · Antiemetic · 5-HT_3 receptor antagonist · Granisetron

Introduction

Radiotherapy is a local treatment modality that aims to destroy target tissue cells. It is frequently used to treat solid malignancies, although it can also be used in the treatment of leukaemia [42] and lymphoma [41]. It is used in definitive, adjuvant or neoadjuvant curative treatment settings as well as in palliative situations. In Germany, two-thirds of all cancer patients treated in palliative situations will need a radiotherapeutic treatment during the course of their disease [49].

With new developments in radiooncology, progress in oncological imaging methods, introduction of new generations of linear accelerators and application techniques including intensity-modulated radiotherapy (IMRT), it is possible to apply high radiation doses to tumours while protecting at-risk organs. Therefore, potential side effects of radiotherapy can increasingly be minimized. Nevertheless, there are patients who experience unpleasant side effects, including radiation-induced nausea and vomiting (RINV), one of the most distressing symptoms in tumour patients undergoing radiotherapy. Persistent untreated nausea and vomiting (emesis) can cause physiological changes such as dehydration, electrolyte imbalance and malnutrition, affect patients' quality of life and even lead to patients refusing further specific therapy.

Such distressing symptoms and their physiological sequelae are particularly concerning in elderly patients. Older patients may already be at an increased risk of dehydration as the thirst reflex decreases with age [24], and cognitive decline may be exacerbated by the physiological effects of uncontrolled nausea and vomiting. With cancer incidence and mortality highest in those aged 65 years and older [54], the radiation oncologist needs to pay particular attention to this patient group. Clearly, prevention of nausea and vomiting should be a priority for any clinician providing radi-

ation therapy. The emetogenic potential of radiotherapy depends, in part, on the dose and volume of radiation, the schedule of administration, the topographic site, and volume of the body irradiated (Table 1), and on individual patient characteristics. The risk of patients experiencing RINV is much greater if the radiation is delivered as a single high dose than if it is fractionated with low doses [16], and is also greater with short intervals between the fractions, with larger field sizes, and with the simultaneous administration of chemotherapy. In addition, the risk of emesis is higher in female patients, in those younger than 50 years and in those who have a history of poorly controlled emesis during previous radio- or chemotherapy [16, 22]. In contrast, a high alcohol intake may reduce the individual risk of emesis [16].

Acute RINV occurs following an asymptomatic latent period of between 30 min and 4 h, which tends to be shorter with higher dose single-fraction radiation [16, 44]. The incidence of RINV is highest during the first 24 h after irradiation. While unlikely, prolonged emesis lasting up to 2–3 days has been reported in up to 40% of patients with highly or moderately emetogenic radiotherapy [16, 44]. Yet there are still unanswered questions regarding the duration of RINV.

The mechanism of RINV is similar to that of chemotherapy-induced nausea and vomiting (CINV) in that exposure to either chemotherapeutic agents or radiation results in release of serotonin (5-hydroxytryptamine, 5-HT) from enterochromaffin cells located in the gastrointestinal (GI) mucosa (Fig. 1). The serotonin released interacts with 5-HT_3 receptors located both peripherally on vagal afferent neurons and centrally in the nucleus tractus solitarius, to elicit the vomiting reflex [28]. RINV occurs most commonly when the GI tract is partially or fully within the irradiated volume, probably because the emetic response is initiated in this region (plexus solaris). The larger the amount of GI tract irradiated (particularly for fields that include the small intestine and stomach), the higher the potential for nausea and vomiting.

External beam radiotherapy is generally perceived by clinicians and patients as less emetogenic than chemotherapy. Yet cancer radiation therapy, with or without chemotherapy, can have a profound impact on the risk of patients experiencing nausea and vomiting. As with chemotherapeutic regimens, there is a well-established risk scale for emetogenicity of radiotherapy. For example, the majority of patients without antiemetics receiving upper abdominal and total body irradiation (TBI) do experience severe RINV [16]. In a fractionated radiotherapy course, where the radiation dose is lower than in single high-dose radiotherapy, radiotherapy may involve up to 30 fractions over 4–6 weeks, and control of emesis during this extended period will be critical for ensuring patient compliance in completing this potentially life-saving treatment. Furthermore, combined treatment modalities involving radiotherapy, chemotherapy and surgery in a variable sequence are becoming increasingly common in oncology in an effort to maximize efficacy in terms of destroying tumour cells and to improve patient survival rates.

Data and physician surveys show that approximately one-third of radiation therapy patients also receive chemotherapy simultaneously or sequentially. While it is commonly assumed in the USA that the oncologist or haematologist

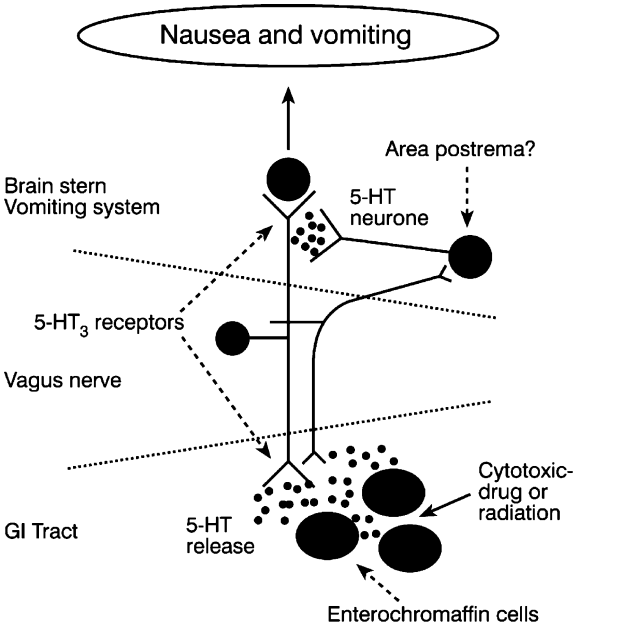

Fig. 1 Effect of 5-HT_3 receptor antagonists on the initiation of RINV and CINV in the GI tract. Reproduced with permission from Freeman et al. [17]

Table 1 Emetic risk category related to area of the body receiving radiation and treatment guidelines

Emetic risk category	Area receiving radiation	Antiemetic guideline
High	Total body irradiation	Before each fraction: 5-HT_3 receptor antagonist+dexamethasone
Moderate	Upper abdomen	Before each fraction: 5-HT_3 receptor antagonist
Low	Lower thorax, pelvis, cranium (radiosurgery), craniospinal	As needed: 5-HT_3 receptor antagonist
Minimal	Head and neck, extremities, cranium, breast	As needed: dopamine receptor antagonist or 5-HT_3 receptor antagonist

From MASCC [30] (www.mascc.org)

will determine the antiemetic therapy in patients treated with combined radiation and chemotherapy, the radiation oncologist or specialist will also be involved in these supportive care decisions. In Europe, however, the radiation oncologist will be the primary decision maker for patients receiving simultaneous radiochemotherapy. Furthermore, the radiation oncologist will be the primary antiemetic decision maker for the remaining two-thirds of radiotherapy patients who do not receive chemotherapy, and surveys have demonstrated that such patients often receive no preventive antiemetic therapy (ISIS therapy monitor).

It is clear, therefore, that the individual risk of a patient experiencing RINV should be carefully considered prior to the initiation of any oncology regimen. Antiemetics are most useful when given prophylactically, with prevention of symptoms being easier than control. Current guidelines recommend preventive treatment with a 5-HT_3 receptor antagonist with or without dexamethasone for each day of therapy for patients receiving highly or moderately emetogenic radiotherapy (Table 1) [30]. Another factor to be considered is the possible risk of anticipatory emesis experienced by the patient in subsequent courses of radiotherapy as a result of poor emetic management in prior courses, highlighting the importance of selecting the most effective antiemetic in the first treatment fraction during the first course of radiotherapy.

5-HT_3 receptor antagonists act by blocking 5-HT_3 receptors and thus preventing the initiation of the emetic response [17]. Since their introduction, these agents have dramatically improved antiemetic treatment, with higher efficacy, fewer side effects and better tolerability over standard antiemetics. Granisetron and ondansetron are the only two 5-HT_3 receptor antagonists that are currently indicated for the control of RINV. Since their introduction in the early 1990s several clinical trials have addressed their efficacy and safety, either with no comparator or versus placebo or conventional treatments such as the dopamine receptor antagonist metoclopramide. No trials have directly compared the efficacy of these agents in a head-to-head trial with efficacy as the primary endpoint. The clinical experience with granisetron, one of the first 5-HT_3 receptor antagonists to be developed, in RINV is reviewed in this paper, and the efficacy of this agent is compared with that of other antiemetic therapies.

Granisetron and other 5-HT_3 receptor antagonists for the control of RINV

What do we expect from an optimal antiemetic?

It should be suitable for use in patients of all ages, safe, easy to administer, i.e. preferably oral and once-daily dosing without side effects or drug–drug interactions should be possible, and have a moderate cost.

Acute RINV

In recent years, a number of studies have demonstrated the high efficacy of the selective 5-HT_3 receptor antagonists for complete or major control of RINV compared to conventional antiemetic agents (e.g. metoclopramide or corticosteroids). Consequently, 5-HT_3 receptor antagonists are now recommended as the "gold standard" in antiemetic guidelines for moderately/highly emetogenic radiotherapy involving TBI or irradiation of the upper abdomen [30]. Current guidelines do not differentiate between the available 5-HT_3 receptor antagonists. Current perceptions are that the safety and efficacy of theses agents are comparable.

The specific efficacy of granisetron in achieving emetic control in acute RINV has been demonstrated in a number of placebo-controlled and comparative studies. Recently, a large, multicentre, double-blind, randomized trial compared the efficacy of once-daily oral granisetron (2 mg) as prophylaxis for RINV for patients receiving upper abdomen fractionated radiotherapy (10–30 fractions) and placebo. A single daily dose of granisetron proved to be significantly more effective in preventing acute RINV than placebo with >92% of granisetron-treated patients (n=134) achieving complete emetic protection during the first 24 h following abdominal radiation, compared with approximately 60% in the placebo group (P<0.0001) [26] (Fig. 2).

The antiemetic efficacy of granisetron in the control of acute RINV has also been compared with that of metoclopramide plus dexamethasone (plus lorazepam) in a double-blind, randomized study of bone marrow transplant (BMT) recipients (n=30) receiving high dose-rate, single-fraction TBI following chemotherapy. Complete response was defined as no emesis, no more than mild nausea, and no rescue medication. After 24 h, only 13% of patients in the control group demonstrated a complete response to therapy compared with 53% in the granisetron group (P=0.02) [38]. Furthermore, granisetron effectively controls RINV in pa-

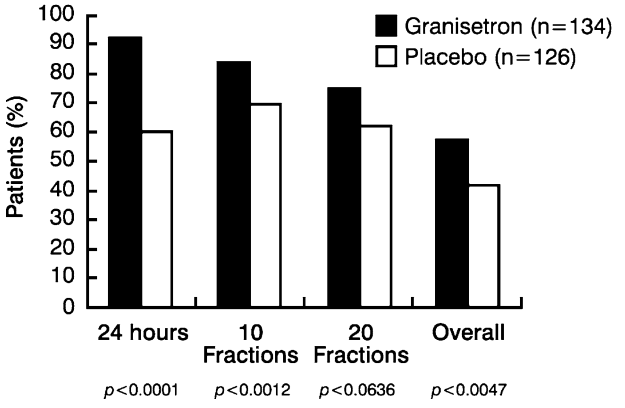

Fig. 2 Percentage of patients with no emesis at 24 h and after 10 and 20 fractions of highly emetogenic upper abdominal radiotherapy after a single daily dose of granisetron or placebo. Reproduced with permission from Lanciano et al. [26]

tients refractory to standard antiemetics [25]. Oral granisetron has been reported to be 100% effective in alleviating emesis from TBI, half-body irradiation, and fractionated irradiation of the pelvis or abdomen after failure of dopamine antagonists [25]. RINV was relieved immediately in 33% of patients (n=15) who had experienced nausea and vomiting due to failed antiemetic therapy with dopamine antagonists, and finally relieved completely in all patients 24–72 h following radiotherapy.

There are a number of clinical trials in which the efficacy of ondansetron has been investigated. Some of these trials did not have a comparator antiemetic regimen; the remainder were versus placebo or conventional agents such as metoclopramide or prochlorperazine. In these trials, ondansetron was shown to be effective in the control of RINV during fractionated TBI prior to chemotherapy, achieving complete control in 44% (11/25) of patients [48]. A number of studies have also demonstrated that ondansetron is more effective than placebo in this group of patients [27, 50]. Franzen et al. [18] reported that 67% of patients receiving ondansetron had complete control of emesis after fractionated radiotherapy to the abdomen compared with 45% of those receiving placebo (P<0.05). Compared with prochlorperazine (10 mg orally three times daily), ondansetron (8 mg orally three times daily) has been shown to have superior efficacy in terms of complete control of vomiting (61% vs 35%, ondansetron vs prochlorperazine; P=0.002) in patients undergoing fractionated radiotherapy to the upper abdomen (more than five daily treatments) [39]. However, in this study, ondansetron did not provide significant benefit over prochlorperazine in terms of nausea control (76% vs 71% of patients with less than five episodes on worst day of treatment, ondansetron vs prochlorperazine), highlighting the difficulty in controlling this symptom. Other studies have also shown ondansetron to be effective against RINV following radiotherapy to the upper abdomen, single-dose radiotherapy, fractionated radiotherapy, TBI or half-body irradiation versus metoclopramide, prochlorperazine or chlorpromazine [40, 43, 52].

Although not approved for the prevention and treatment of RINV, both dolasetron and tropisetron have been investigated in some clinical trials. Dolasetron has been shown to be superior to placebo for the control of acute RINV caused by single high-dose radiotherapy to the upper abdomen [6]. A further study has shown that dolasetron provides major or complete control in the majority of patients receiving TBI and cyclophosphamide chemotherapy [15]. Patients receiving tropisetron have been shown to experience less nausea and vomiting than patients receiving metoclopramide after abdominal radiotherapy for non-metastatic seminoma stage I [2]. Furthermore, in a comparison of metoclopramide and tropisetron used as rescue medication following a failed first-round antiemetic trial with metoclopramide, tropisetron controlled symptoms in 73% of patients compared with one-third in the metoclopramide group [32].

As the newest 5-HT_3 receptor antagonist to be marketed, there are no clinical trials investigating the efficacy and safety of palonosetron for the control or prevention of RINV.

Delayed or prolonged RINV

Delayed or prolonged emesis, beginning about 24 h after therapy and possibly continuing for several days, is less common in patients receiving radiotherapy than those receiving cisplatin or cyclophosphamide-based chemotherapy. However, some patients continue to experience nausea and vomiting for some considerable time after radiotherapy and some days after being discharged from hospital. Thus, delayed RINV is an important aspect of quality of life and should be considered in terms of minimizing both the patient's discomfort and the risk of patient withdrawal from the treatment protocol. Controlled studies assessing the effectiveness of different 5-HT_3 receptor antagonists in combination with dexamethasone or metoclopramide are in progress. The new NK_1-receptor antagonist, aprepitant, is currently indicated for CINV in combination with a 5-HT_3 receptor antagonist and dexamethasone but has yet to be investigated for RINV.

Convenience of a once-daily dosing regimen

In general, a single daily dose antiemetic is most convenient for patient comfort and compliance with radiotherapy. Granisetron has an elimination half-life of between 9 and 12 h in cancer patients [19] and displays insurmountable binding at 5-HT_3-receptors [10], with once-daily dosing providing control of nausea and vomiting symptoms for at least 24-h after treatment. Although not a direct head-to-head trial, the efficacy of a single daily dose of granisetron (2 mg orally) has been compared with that of a three times daily dose of ondansetron (8 mg ×3) in a double-blind, randomized trial of patients (n=34) receiving a highly emetogenic regimen of hyperfractionated TBI before BMT, and the number of emetic episodes in these patients was also compared with the number of episodes in a historic control group of 90 patients receiving no 5-HT_3 receptor antagonist therapy. Significantly more patients receiving a single daily dose of granisetron (61.1%) or three-times daily ondansetron (46.7%) had no emetic episodes in the first 24 h compared with those receiving no 5-HT_3 receptor antagonist (6.7%; P<0.01) [51]. Furthermore, over the 4-day study significantly more patients were emesis-free in the granisetron (33.3%) and ondansetron (26.7%) groups than in the control group (0%, P<0.01; Fig. 3) [51].

As noted above, the upper abdomen is a critical site for the initiation of emesis: radiotherapy to the upper abdomen causes RINV in 30–90% of patients [47]. A prospective randomized trial of ondansetron given 8 mg twice daily

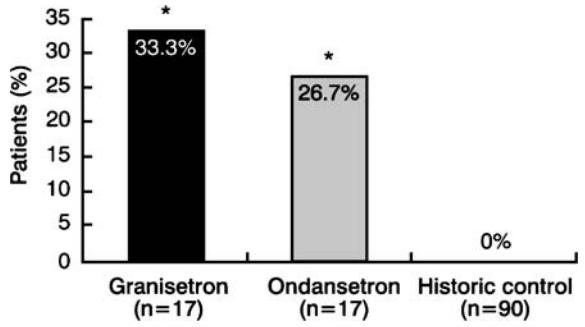

Fig. 3 Proportion of patients receiving hyperfractionated TBI who experienced no emetic episodes over the 4-day period after once-daily granisetron (2 mg) or ondansetron (3×8 mg) (n=34) vs a historic control group (n=90). Reproduced from Spitzer et al. [51]. *P<0.01

showed good antiemetic potential following fractionated radiotherapy including the abdomen compared to placebo (complete response in 67% vs 45% of patients, respectively) [18]. Similarly, another study of upper abdomen irradiation in 30 patients showed that increasing doses of ondansetron (from 4 to 8 mg) with increasing doses of radiotherapy effectively controlled RINV, but the higher doses of radiation required twice-daily dosing with ondansetron to control the symptoms of emesis [31]. In contrast, equal efficacy of once-daily dosing of granisetron at two different dosing regimens (20 vs 40 μg/kg i.v.) was shown in patients receiving single high dose-rate radiotherapy to the lower half-body [29]. In general, under circumstances where a prolonged onset of RINV is expected, either with high doses of radiation or with doses that are fractionated throughout the day (e.g. hyperfractionation), and when it is likely that symptoms may be experienced after discharge, an antiemetic with a long duration of action is preferred.

Combination chemotherapy and radiotherapy

Many conditioning regimens for BMT recipients use a combination of high-dose chemotherapy and radiotherapy. Granisetron as a single-dose agent has been shown in a number of studies to be highly effective in controlling nausea and vomiting associated with high-dose chemotherapy and radiotherapy prior to BMT [5, 33, 38].

In a study reported by Okamoto et al. [33], granisetron was shown to display superior control of nausea and vomiting in comparison with standard antiemetics (based on metoclopramide) in patients treated with a combination of chemo- and radiotherapy before hematopoietic stem cell transplantation (HSCT). Granisetron was given intravenously starting 30 min before each dose of chemotherapy or single-dose as well as fractionated TBI and was repeated 12 h after treatment. During the first 24 h of conditioning, 87.1% of patients achieved major emetic control (three or fewer emetic episodes) compared with 37% receiving standard therapies based on metoclopramide (P<0.001) [33]. Furthermore, the number of patient days with complete and major emesis control was significantly higher in the granisetron group than in the control group (P<0.001; Fig. 4).

Similar results with granisetron have been reported for other studies of TBI after chemotherapy before BMT. For example, granisetron has been shown to result in complete emetic control during the 12 h following single-dose TBI in 78% of BMT recipients who had received chemotherapy prior to TBI [5]. A further study showed complete emetic control in 53% of granisetron-treated patients during the first 24 h after single-dose TBI following chemotherapy [38]. A comparative single-centre, randomized study has shown granisetron and ondansetron to be equally effective in controlling emesis during BMT conditioning [34]. In this trial of 187 patients receiving combined TBI and chemotherapy for their first BMT, complete emetic control was seen >60% of patients for both agents [34]. Granisetron plus dexamethasone has also been shown to provide effective and well-tolerated control of RINV in 98% of patients during BMT conditioning involving the application of high-dose cyclophosphamide chemotherapy and TBI [3, 4].

Safety, tolerability and drug–drug interactions

Granisetron is a potent and highly selective 5-HT_3 receptor antagonist. Granisetron binds irreversibly, and with high affinity, to the 5-HT_3 receptor and exhibits little or no affinity for other receptors, including other types of serotonergic receptors (dopaminergic, adrenergic, benzodiazepine or opioid receptors) [8]. This contrasts with the competitive antagonism exhibited by ondansetron at 5-HT_3 receptors and its detectable affinity (pK_i >5) for other serotonergic receptors (5-HT_{1B}, 5-HT_{1C}), α-adrenergic and μ-opioid receptors [53]. The irreversible binding of granisetron coupled with its prolonged half-life might explain the efficacy

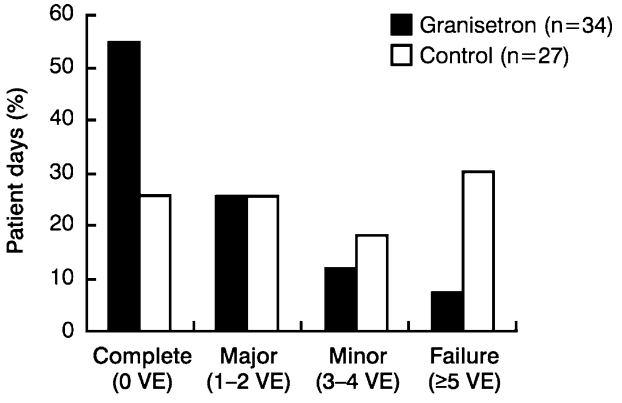

Fig. 4 Emesis control expressed as patient days in patients receiving granisetron or standard antiemetics (control group) during conditioning for stem cell transplantation. Reproduced with permission from Okamoto et al. [33]. *VE* vomiting episodes

of a once-daily dose of the agent in the 24-h control of RINV.

Cancer patients receiving palliative treatment have been reported to take an average of five or more further medications for symptom relief [12] and also frequently take multiple medications for comorbid illnesses, with or without the knowledge of the physician or nurse. Such polypharmacy is particularly common in elderly cancer patients as they have an increased likelihood of having other comorbid conditions for which they are also receiving medication [14]. It is clear, therefore, that the potential for drug interactions with other coadministered medications should be considered prior to antiemetic drug selection.

A study of drug interactions in patients in a hospital emergency department found that the risk of adverse drug interactions rose from 13% with patients taking two medications to 82% for those taking seven or more medications [20]. Particular care needs to be taken in elderly patients when treating with pharmacotherapy due to metabolic differences in this population and an increased incidence of comorbid conditions and concomitant therapies.

Granisetron is metabolized by a single cytochrome P450 subfamily (CYP3A) [7], while the other 5-HT_3 antagonists are metabolized by a number of different hepatic enzymes (Table 2) [13, 46]. Inhibition or induction of hepatic enzymes may increase the risk of interactions. Enzyme induction can result in accelerated enzyme synthesis, faster drug metabolism and subtherapeutic drug concentrations. Enzyme inhibition, however, may slow drug metabolism leading to accumulation of drug levels in plasma and an exaggerated or prolonged response with an increased risk of toxicity [21]. In addition to being metabolized by just one isozyme subfamily, granisetron has not been shown to induce or inhibit hepatic metabolism [7, 9]. Additionally, granisetron is the only commonly available 5-HT_3 receptor antagonist whose metabolism does not involve the polymorphic isozyme CYP2D6. CYP2D6 genetic polymorphism results in four different phenotypes (poor, intermediate, extensive and ultra-rapid metabolizers), which leads to varying rates of drug metabolism between individuals. Depending on phenotype, an individual may metabolize a drug very rapidly (ultra-rapid metabolizers) potentially leading to reduced drug efficacy. This has been demonstrated in a study by Kaiser et al. [23], who showed reduced emetic control in genetically defined ultra-rapid metabolizers of ondansetron and tropisetron. Conversely drug plasma levels may be raised in poor (slow) metabolizers, which may increase the potential for drug–drug interactions and adverse effects or reduce the efficacy of drugs that require conversion to an active metabolite.

Table 2 Cytochrome P450 enzymes involved in the metabolism of common 5-HT_3 receptor antagonists

	CYP1A1	CYP1A2	CYP2D6	CYP3A3/4/5
Granisetron				✓
Ondansetron	✓ (minor)	✓	✓	✓
Dolasetron			✓	✓
Tropisetron			✓	✓ (minor)

Reproduced with permission from Blower [9]

Granisetron has been reported to be safe and well tolerated in many clinical studies investigating RINV [3, 4, 26, 34, 38, 51]. The most common adverse effects are reported to be headache and diarrhoea, although most headaches are mild-to-moderate in severity, and respond to analgesic therapy. In trials investigating the control of CINV, granisetron has been shown to be associated with a lower risk of inducing dizziness and abnormal vision than ondansetron [36, 37]. This difference may be a consequence of peripheral receptor binding, which does not occur with granisetron [10]. However, these trials investigated ondansetron at a dose of 32 mg i.v., a dose not indicated or recommended for the treatment of RINV.

The safety and tolerability of any antiemetic agent is important in every patient, but is of particular concern in certain patient groups, including patients demonstrating a greater susceptibility to adverse effects (e.g. elderly or paediatric patients) and patients with comorbid conditions. The occurrence of comorbid cardiovascular disease in some cancer patients is of concern, especially if the patient is receiving radio- and/or chemotherapy, since both can have an influence on cardiac function [11, 45]. In cases where radiation-induced cardiac effects have been noted, the site of irradiation was generally most of the myocardium [45]. The most common effects reported include acute pericarditis, chronic pericardial fibrosis, chronic myocarditis, valvular insufficiencies and conduction disturbances [45]. Although radiation-induced cardiotoxicity in case of chest irradiation is very rarely acute, cardiovascular safety of the 5-HT_3 receptor antagonists should be highlighted as a treatment consideration, given the high proportion of elderly patients who are likely to be suffering some degree of cardiac impairment. In addition, if patients are receiving multiple concomitant medications that have minor cardiovascular effects when administered on their own, there is always a risk of cumulative toxicity. No cardiovascular warnings are associated with granisetron, and the cardiovascular safety of the agent has been demonstrated in RINV patients receiving single-dose lower half-body radiotherapy [29]. No clinically significant effects on cardiac parameters have been seen with granisetron [1]. In addition, no dosage adjustment of the agent is required in patients with hepatic or renal impairment [35].

Discussion

In summary, selective 5-HT_3 receptor antagonists are the agents of choice for the control of moderately or highly emetogenic RINV with or without corticosteroids [30] and should, therefore, be used as standard prophylaxis to pre-

vent nausea and vomiting in patients at moderate and high risk of RINV. Physicians should select the agent best suited to the needs of their patients, one with proven clinical efficacy, dosing convenience and no additive complications. A single oral or i.v. dose of granisetron can control symptoms of RINV for at least 24 h, and a high proportion of patients (61–92%) undergoing highly emetogenic TBI achieve complete emetic control during granisetron therapy [26, 38, 51]. The 24-h control of nausea and vomiting with a single daily dose should aid patient compliance throughout therapy and thereby contribute to improving quality of life.

Current treatment protocols frequently recommend multimodal therapy strategies so that often patients undergo surgery in combination with adjunctive chemotherapy and radiotherapy. The selection of the most appropriate antiemetic regimen should thus consider risk factors for all combined therapies. The effectiveness of granisetron as a single agent for complete or major control of acute RINV has been demonstrated in many studies involving combination radiotherapy and chemotherapy [5, 33, 34, 38]. Furthermore, granisetron has a good tolerability profile, low risk of drug interactions and good cardiovascular safety [29]. As there are a limited number of clinical trials, many of the considerations for antiemetic therapies discussed in this review are hypothetical (for example potential for drug interactions, cardiovascular safety, tolerability profile related to extra 5-HT_3 receptor binding), and as a result, antiemetic guidelines do not distinguish between the different agents in terms of safety and efficacy. Nevertheless, these differences may translate into clinical differences in certain patient groups, such as the elderly. Clinical trials investigating these aspects are awaited.

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