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REVIEW

Ronald de Wit · Matti Aapro · Peter R Blower

Is there a pharmacological basis for differences in 5-HT_3-receptor antagonist efficacy in refractory patients?

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Abstract 5-HT_3-receptor antagonists are the current antiemetic 'gold standard' for chemotherapy- and radiotherapy-induced nausea and vomiting. Interestingly, studies have shown that patients experiencing poor control of acute chemotherapy-induced nausea and vomiting with one antiemetic therapy may respond well to another agent, including a drug of the same class. This review examines pharmacological differences between the 5-HT_3-receptor antagonists in order to determine potential reasons for their differing efficacy, particularly in relation to refractory emesis. Differences in drug metabolism by the cytochrome P450 system, inadequate dosing of the respective agents, differences in onset and duration of action, and effects on serotonin release and reuptake are discussed.

Keywords 5-HT_3-receptor antagonists · Chemotherapy-induced nausea and vomiting · Refractory emesis

Introduction

Considerable progress has been made in the prevention of acute cytotoxic-induced emesis over the last decade, largely as a result of the introduction of the 5-HT_3-receptor antagonists. When used in combination with corticosteroids these agents result in complete protection from acute-onset emesis in between 70% and 80% of patients receiving highly emetogenic chemotherapy [25]. Nevertheless, this still leaves a sizeable proportion of patients who continue to experience refractory emesis, despite receiving antiemetic prophylaxis with a 5-HT_3-receptor antagonist. Although refractory emesis has not been precisely defined, it has been described in some studies as "*emesis in the previous cycle of chemotherapy [or radiotherapy] but without emesis before the subsequent cycle of chemotherapy (no anticipatory emesis)*" [43]. Since patients with poor control of acute chemotherapy-induced nausea and vomiting are more likely to experience delayed emesis and/or anticipatory symptoms in subsequent treatment cycles [52], refractory emesis presents a considerable challenge for clinicians.

Studies have demonstrated that patients receiving chemotherapy or radiotherapy who are refractory to one antiemetic therapy can respond well to another antiemetic treatment regimen [7, 10, 15, 40, 47, 50, 57]. For example, in one study, 52% of patients refractory to treatment with standard antiemetics (including dopamine antagonists and corticosteroids) were shown to achieve effective control of emesis following treatment with the 5-HT_3-receptor antagonist tropisetron [7]. Control of emesis has also been demonstrated in patients refractory to standard antiemetics following a switch to the 5-HT_3-receptor antagonists ondansetron [47] and granisetron [50]. Of specific interest, however, are studies that have shown effective treatment of refractory emesis in patients after switching from one 5-HT_3-receptor antagonist to another, particularly when ondansetron-treated patients are switched to receive granisetron in subsequent cycles [10, 15, 57]. It was previously assumed that since agents in the 5-HT_3-receptor antagonist drug class share similar chemical structures and interact with the same receptor, patients refractory to one 5-HT_3-receptor antagonist may not respond to another. Yet the success of this strategy has been provided as evidence for a lack of "cross resistance" between these agents [15].

In recent years, it has become clear that patients' risk of experiencing cytotoxic-induced emesis is complex and

R. de Wit (✉)
Rotterdam Cancer Institute,
Groene Hilledijk 301, 3075 Rotterdam,
The Netherlands
E-mail: r.dewit@erasmusmc.nl

M. Aapro
Clinique de Genolier,
1272 Genolier, Switzerland

P. R Blower
Poole House, Great Yeldham,
Halstead, Essex, CO9 4HP, UK

dependent not only on the emetogenic potential of the treatment regimen and the emetogenic risk profile of the individual, but also on the characteristics of the antiemetic agent used [1, 17, 24, 30, 39]. In light of this understanding, this short review examines the potential reasons behind why some 5-HT_3-receptor antagonists may offer effective control of nausea and vomiting in patients who are refractory to antiemetic treatment, including other 5-HT_3-receptor antagonist agents.

Crossover between 5-HT_3-receptor antagonists in refractory patients

A number of studies have demonstrated that cancer patients undergoing chemotherapy or radiotherapy regimens who are refractory to other antiemetic therapies respond well to subsequent treatment with serotonin antagonists. In one randomized, double-blind, crossover study, the antiemetic efficacy of granisetron, 1 mg/day, plus dexamethasone, was compared with that of high-dose metoclopramide, 0.5–1.0 mg, plus dexamethasone, in patients receiving cyclophosphamide, hydroxydaunomycin, oncovin and prednisone (CHOP) therapy; 58.3% of patients who did not respond to initial therapy with metoclopramide responded well to granisetron [50]. The efficacy of granisetron, 1 mg/day, in patients refractory to therapy with dopamine antagonists has also been demonstrated in a small study of 15 patients receiving radiotherapy; upon switching to granisetron, one-third of patients had immediate remission of symptoms, and all patients experienced remission of symptoms within 3 days [40].

Although evidence for the success of 5-HT_3-receptor antagonists, such as dolasetron, ondansetron and palonosetron, following a failure with another agent in this class have not been reported in the literature to date, studies have shown that patients who have previously failed ondansetron antiemetic therapy can be successfully treated with granisetron in subsequent cycles [10, 15, 57]. Carmichael et al. [10] studied 456 patients receiving chemotherapy who had failed to achieve control of emesis with other antiemetics in previous cycles of therapy, 85 of whom were refractory to ondansetron. Following treatment with granisetron, 3 mg, 38, 45 and 58% achieved complete control of nausea and vomiting during three subsequent chemotherapy cycles. Overall, more patients receiving non-cisplatin-based chemotherapy regimens experienced a complete response (59.3–67.9%) compared with patients treated with cisplatin (>50 mg/m^2 ; 25.0–57.1%). In a second study, of 517 chemotherapy-treated patients, 87 were found to have failed ondansetron treatment due to lack of antiemetic efficacy; of these patients, 38% achieved a complete response to granisetron in the subsequent chemotherapy cycle [57]. Another double-blind, randomized study by de Wit et al. [15] examined 45 patients receiving highly or moderately emetogenic chemotherapy who had failed to achieve antiemetic protection with ondansetron plus dexamethasone. Patients were randomized to receive continued treatment with ondansetron, 8 mg, or crossover treatment with granisetron, 3 mg, with both groups also receiving dexamethasone, 10 mg. Of the patients switched to granisetron, 47% exhibited a complete response compared with only 5% of patients who remained on ondansetron.

Possible explanations for successful crossover between 5-HT_3-receptor antagonists

Due to the similarity in the pharmacological selectivity and clinical profiles of the 5-HT_3-receptor antagonists, it has been suggested previously that antiemetic failure with one agent would predict subsequent failure to all 5-HT_3-receptor antagonists [25, 30]. However, the studies outlined above demonstrate that this assertion may not be correct when granisetron is used in patients who have failed ondansetron therapy. Although ondansetron and granisetron belong to the same drug class and have demonstrated equivalent efficacy in comparative trials [48, 51, 54], 5-HT_3-receptor antagonists differ in their pharmacology, which may explain the efficacy of one agent and failure of another in the same patient.

There is a need to further investigate, in blinded controlled clinical trials, the responsiveness of individual patients to different 5-HT_3-receptor antagonists. However, due to the lack of published data detailing effective crossover from alternative 5-HT_3-receptor antagonists, the discussion in the following section of this review will focus on the published data available at this time, which reports on the use of granisetron in patients refractory to ondansetron.

Differences in cytochrome P450 metabolism of 5-HT_3-receptor antagonists

It has recently been postulated that the efficacy of granisetron in patients refractory to ondansetron therapy may be due to the fact that it is not metabolized through the hepatic cytochrome P450 (CYP) enzyme 2D6 [14]. This is because the CYP2D6 enzyme is subject to genetic polymorphism, producing four distinct phenotypes that range from poor to ultra-rapid metabolizers, with extensive and intermediate metabolizers falling in between [35]. Poor metabolizers have slowed drug metabolism, leading to an accumulation of high levels of unmetabolized drugs and increased duration of adverse events and increased potential for drug–drug interactions [13]. Conversely, ultra-rapid metabolizers have enhanced drug metabolism, potentially resulting in loss of therapeutic efficacy when agents are used at conventional doses [13]. Although the prevalence of ultra-rapid metabolizers in the general population receiving cancer chemotherapy is low, recent data indicate that patients of the CYP2D6 ultra-rapid metabolizer phenotype have an increased risk of developing severe acute

chemotherapy-induced nausea and vomiting following moderate-to-high-emetogenic chemotherapy regimens when receiving antiemetics metabolized by this enzyme [39]. Ondansetron is partially metabolized by CYP2D6, in addition to CYP1A1, CYP1A2, and the CYP3A family [5, 16]. Consequently, ondansetron could, potentially, be metabolized at a faster rate in patients who are ultra-rapid metabolizers of CYP2D6, lowering the serum concentration of the agent to sub-optimal levels, resulting in antiemetic failure. Indeed, in one study, patients treated with ondansetron who were identified as ultra-rapid metabolizers of this isozyme were found to have a significantly higher frequency of vomiting in the first 4 h ($P < 0.001$) and 5–24 h ($P < 0.03$) after chemotherapy than patients without this phenotype (Fig. 1) [39]. In contrast, the metabolism of granisetron does not involve CYP2D6, being metabolized by members of the CYP3A sub-family only [3, 5]. Granisetron is thus less likely to be subject to variations in efficacy, which may explain the success of the agent in patients refractory to treatment with ondansetron.

Dosing of 5-HT_3-receptor antagonists

An alternative explanation for the potential efficacy of granisetron in ondansetron failures may be the doses of the agents employed in the studies. For example, in the study by de Wit et al. [15], ondansetron was administered as a single dose (8 mg i.v.) in combination with dexamethasone. Some studies have shown this dose of ondansetron to be effective prophylaxis for patients undergoing emetogenic chemotherapy regimens [34, 54, 56]. However, there is also evidence to suggest that this dose may be sub-optimal in some patients [2, 6, 32, 36, 58].

In one study, ondansetron, 8 mg i.v. once daily, was shown to provide less antiemetic protection than ondansetron, 32 mg i.v. once daily, in patients receiving either moderately or highly emetogenic chemotherapy regimens [2]. Of the patients receiving highly emetogenic chemotherapy, significantly fewer of those receiving ondansetron, 8 mg i.v. once daily, than ondansetron, 32 mg i.v. once daily, experienced a complete response rate (no emetic episodes; 35% vs. 48%, $P = 0.048$), while more of these patients had emetic episodes ($P = 0.015$) and a higher failure rate (> 5 emetic episodes or required rescue medication; 39% vs. 20%, $P = 0.018$). In that same study, ondansetron, 8 mg i.v. once daily, also produced a significantly inferior antiemetic response for all primary and secondary variables compared with ondansetron, 32 mg i.v. once daily ($P < 0.05$) in patients receiving moderately emetogenic chemotherapy [2]. A further study has reported that fewer patients receiving ondansetron, 8 mg i.v., than 32 mg i.v. (both combined with dexamethasone), achieved a complete response (no vomiting) on the first day after high-dose cisplatin chemotherapy (14% vs. 45%; $P = 0.0001$) [58]. Furthermore, in this study, 17% of patients receiving low-dose ondansetron experienced antiemetic failure (> 5 vomiting episodes) compared with 5% of those receiving ondansetron, 32 mg.

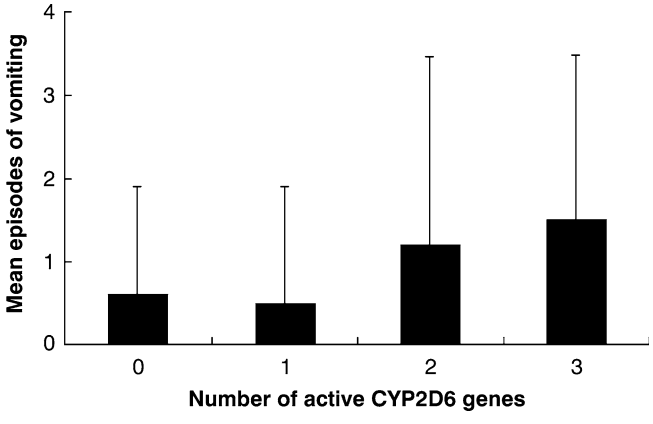

Fig. 1 Mean number of episodes of vomiting (± SD) as a function of the number of active CYP2D6 genes experienced 5–24 h after chemotherapy in patients receiving ondansetron, 8 mg twice daily. Reproduced by kind permission of the American Society of Clinical Oncology from Kaiser et al. [39]

The suggestion that a single dose of ondansetron, 8 mg, may provide sub-optimal antiemetic efficacy in some patients is supported by the findings of a recent retrospective analysis of the antiemetic protection experienced by 224 female breast cancer patients receiving cyclophosphamide-containing regimens in the USA between 1998 and 2002 [23]. In this analysis, significantly fewer patients receiving ondansetron, 8 mg i.v., experienced total control of emesis than those receiving either ondansetron, 32 mg, or granisetron, 10 μg/kg or 1 mg (42.6% vs. 64.5% and 67.5%, respectively; $P < 0.01$). Low-dose ondansetron (8 mg) has also been shown to be less effective than granisetron, 3 mg, in patients receiving moderately emetogenic chemotherapy; significantly more granisetron-than ondansetron-treated patients experienced complete control during the first 24 h after chemotherapy (80.0% vs. 68.5%; $P = 0.034$) [36]. In addition, a recent meta-analysis of three non-cisplatin-based studies [36, 44, 59] comparing ondansetron, 8 mg i.v. once daily, with granisetron, 3 mg i.v., for the complete prevention of acute vomiting, has reported a significant advantage for granisetron ($P = 0.041$) [37]. This analysis, which included only randomized studies, involved patient numbers ranging from 54 [59] and 60 [44] to 161 [36]. A significant advantage for granisetron, based on odds ratios calculated for each of the individual studies assessed, was observed by both Jantunen et al. [36] ($P < 0.01$) and Yalçin et al. [59] ($P < 0.05$), producing a pooled odds ratio of approximately 0.5 ($P = 0.041$); this was despite the lack of any statistical difference between granisetron and ondansetron in the control of acute vomiting reported by Massidda and Ionta [44]. A further meta-analysis including data from ten additional randomized studies comparing ondansetron, 8 mg i.v.,

versus granisetron, 3 mg i.v., showed a possible advantage for granisetron in patients receiving non-cisplatin-based regimens ($P < 0.05$) [38]. Additionally, dosing sub-analyses showed a possible inferiority of ondansetron, 8 mg, versus ondansetron, 24/32 mg, in cisplatin-based regimens ($P < 0.05$), while no significant difference between granisetron, 3 mg or 40 μg/kg, or 1 mg or 10 μg/kg, was observed.

The above-mentioned studies may indicate that ondansetron, 8 mg once daily, does not provide adequate protection from chemotherapy-induced nausea and vomiting in some patients. Therefore, another explanation for the successful crossover from ondansetron to granisetron may be partly due to 5-HT_3-receptor antagonist dosing aspects, i.e. greater efficacy provided by granisetron, 3 mg [15]. The use of blinded, dose-ranging studies accompanied by pharmacokinetic analysis of drug levels in refractory patients, would help to further establish the extent of dosing on the duration of response of the various 5-HT_3-receptor antagonists.

Duration of action

A further consideration in the assessment of antiemetic efficacy is the fact that chemotherapeutic agents vary in the onset and duration of their emetic action [30, 55]. For example, the onset of nausea and vomiting induced by cyclophosphamide is delayed for around 10 h after administration, whereas cisplatin exhibits a biphasic incidence with an initial peak at 4 h and a further peak during days 2–4 (Table 1) [1, 17]. The duration of emesis associated with different cytotoxic regimens also varies, with the emetogenic potential of some treatments lasting for only a few hours and others, (e.g. cisplatin and cyclophosphamide) having a prolonged emetogenic potential lasting up to 5 days [30]. Studies indicate that serotonin, acting on 5-HT_3 receptors, mediates the acute emetic response (defined as the first 24 h after cytotoxic therapy), with non-serotonergic mechanisms being responsible for delayed emesis [31]. The understanding of the involvement of 5-HT_3 receptors in this response led to the development of the 5-HT_3-receptor antagonists, which are widely regarded as the most effective agents in acute emesis [30]. Nevertheless, 5-HT_3-receptor antagonists differ in their duration of action, and thus their ability to provide complete control of emesis throughout the first 24 h may vary according to the antiemetic regimen and the pharmacology of the individual agent used.

Although the duration of action of the 5-HT_3-receptor antagonists at the receptors responsible for emesis is virtually impossible to measure in humans, the inhibition by these agents of the serotonin-mediated cutaneous flare response is a good surrogate [46]. From these early studies in human volunteers, ondansetron was shown to have a duration of action of approximately 9 h, compared with a duration of action of granisetron of greater than 24 h. The prolonged duration of action of granisetron compared with ondansetron is thought to be due to the longer half-life of granisetron (9 h vs. 4 h for ondansetron) [10, 53], coupled with the observation that granisetron displays 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 [49]. The nature of this antagonism by granisetron is thought to underlie the fact that its pharmacodynamic half-life far exceeds its plasma half-life, with effective 24-h antiemetic control being demonstrated following a single administration of the agent [29].

Even though the patient numbers are small, it is interesting to note that in the study by de Wit et al. [15] the response to granisetron in ondansetron-refractory patients is more apparent in patients receiving cyclophosphamide chemotherapy than in those receiving cisplatin (Fig. 2) [4]. Indeed, 29% of ondansetron-treated patients receiving cisplatin responded to subsequent granisetron therapy whereas the response was 58% in the cyclophosphamide group [15]. This difference between cisplatin-based and non-cisplatin-based chemotherapy regimens was also apparent in the study by Carmichael et al. [10]. Given the different patterns of emesis induced by the two chemotherapeutic agents used in this study, the results may be explained in part by the

Table 1 Emetogenic potential and onset of emetic response following administration of cisplatin and cyclophosphamide [1]

	Emetogenic potential	Onset of emetic response (h)
Cisplatin	High >90	1–6
Cyclophosphamide[a]	Moderate 30–60	6–12

[a] High dose

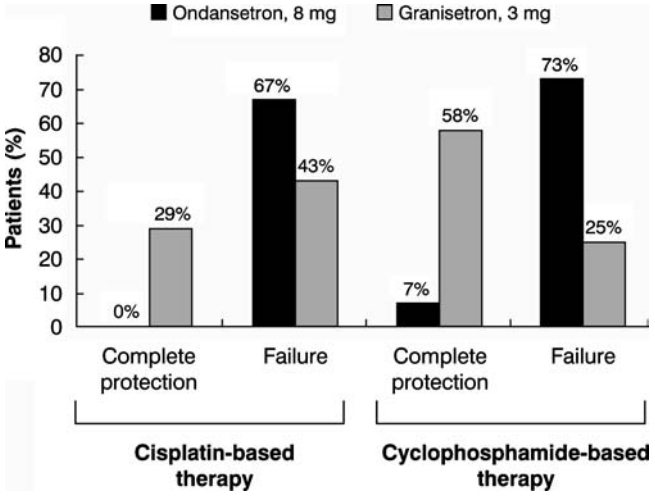

Fig. 2 Percentage of patients crossed over to granisetron, 3 mg, or remaining on ondansetron, 8 mg, achieving complete control of emesis or antiemetic failure [15]

longer duration of action of granisetron providing better efficacy than ondansetron during the late-acute phase (i.e. 12–24 h after therapy), when cyclophosphamide is most emetogenic. This hypothesis is supported by a recent meta-analysis of studies comparing ondansetron, 8 mg i.v., and granisetron, 3 mg i.v., which found superior protection with the use of granisetron in non-cisplatin-based studies, whereas no differences between the agents were apparent in studies employing cisplatin-based regimens [37].

Differences in serotonin concentration at 5-HT_3 receptors in the gastrointestinal tract

Further reasons for antiemetic control by one 5-HT_3-receptor antagonist and failure by another may be linked to their ability to inhibit the release of serotonin in the gastrointestinal tract itself. High concentrations of serotonin at 5-HT_3 receptors in the gastrointestinal system and in the circulation may produce a greater emetic response, and this is likely compounded if competitive receptor antagonism is involved.

Serotonin release from enterochromaffin cells

Evidence suggests that toxic free radical generation (caused by chemotherapy and radiotherapy) within the gut wall activates cholinergic interneurones that, in turn, activate enterochromaffin cells to cause the release of serotonin, which is critical in triggering chemotherapy- and radiotherapy-induced nausea and vomiting [11, 12, 42]. The released serotonin is then free to bind to 5-HT_3 receptors on abdominal afferent nerves [19], which may then stimulate the vomiting reflex via 5-HT_3 receptors located in the sub-nucleus gelatinosus of the nucleus tractus solitarius of the brainstem [41].

Conflicting results regarding the ability of 5-HT_3-receptor antagonists to block release of serotonin from enterochromaffin cells in the gastrointestinal tract have been reported. Investigations using animal models have shown that granisetron, ramosetron and tropisetron, at concentrations as low as 0.1 μM/l, all reduce cisplatin-mediated release of serotonin from enterochromaffin cells [18, 21, 26]. Such inhibition is not reported with ondansetron, even at doses as high as 1 μM/l [26]. Other studies investigating ondansetron show a similar lack of inhibition of serotonin release from enterochromaffin cells [22, 45]. Endo et al. [20], however, have reported the ondansetron-mediated inhibition of serotonin release from isolated ferret ileum, although in a concentration-independent manner, unlike the concentration-dependent inhibition observed with granisetron and ramosetron in the same study. Other studies, by the same investigators and others [22, 45], report no inhibition of serotonin release from enterochromaffin cells in ferret ileum by ondansetron, in contrast to a significant inhibition produced by granisetron in the same model [21]. This inhibition with granisetron is repeated in enterochromaffin cells in the isolated rat ileum [18]. These results suggest a different pharmacological profile for these agents in regard to inhibition of serotonin release from enterochromaffin cells, although the relevance of these preclinical observations to effects in man needs to be established in clinical studies.

Some studies have been carried out in cancer patients using plasma concentration and urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) as markers for serotonin release from enterochromaffin cells [11, 12]. Little inhibition of urinary or blood dialysate 5-HIAA levels has been detected in patients receiving cisplatin following treatment with ondansetron [11, 12] and granisetron [12]. However, urinary 5-HIAA is probably unreliable as a sole indicator of serotonin release from the gastrointestinal system [28]. Evidence suggests that in addition to measurement of plasma 5-HT and urinary 5-HIAA, measurement of conjugated metabolites of serotonin are also necessary to provide acomprehensive picture of gastrointestinal serotonin release [28]. Studies investigating the effects of 5-HT_3-receptor antagonists on levels of these metabolites are needed in order to establish whether these agents exert an effect on serotonin release in addition to antagonism at the 5-HT_3-receptor site.

If the difference in the degree of inhibition by the 5-HT_3-receptor antagonists is confirmed in humans, this might explain how different degrees of antiemetic control are achieved with different 5-HT_3-receptor antagonists in the same patient. A dual action combining inhibition of serotonin release combined with 5-HT_3-receptor antagonism (i.e. competitive vs reversible) may result in more effective antiemetic action. Clinical studies involving the measurement of conjugated metabolites of serotonin, which more aptly reflect release of serotonin from enterochromaffin cells, are warranted.

The serotonin reuptake transporter

The serotonin reuptake transporter (SERT) is essential for the inactivation of serotonin once it has been released from its sites of storage (e.g. enterochromaffin cells) [27]. Genetic polymorphic differences in the SERT have been linked with a number of neuropsychiatric disorders [33] and gastrointestinal disorders such as irritable bowel syndrome (IBS) [8, 27]. Potentially, this could be linked to differences in the inactivation of serotonin by cancer patients receiving emetogenic chemotherapy or radiotherapy regimens. A ‘poor’ transporter will result in a slower uptake of endogenous serotonin, meaning that more remains available outside the cell to induce an emetic response upon binding to 5-HT_3 receptors and to compete with serotonin antagonists. Further studies are required to substantiate this. An interesting observation from research in IBS is that SERT differences may have a gender-based link, since the 5-HT_3-receptor antagonist

alosetron has only been demonstrated to be effective in a subset of female IBS patients, and is not approved for use in male patients [9]. In view of the greater emetic susceptibility of female compared with male cancer patients, this common mechanistic thread requires further clinical investigation.

Conclusions

Although much progress has been made in identifying the treatment and patient factors contributing to an individual's risk of developing cytotoxic-induced nausea and vomiting, it is still not clear why some patients experience antiemetic failure on one antiemetic therapy while other patients may respond well to the same course of treatment. Similarly, while we know that patients experiencing poor control of acute chemotherapy-induced nausea and vomiting are more likely to experience further symptoms in subsequent cycles, antiemetic success or failure in one chemotherapy cycle does not always predict a similar response to the next cycle with the same chemotherapy regimen [52]. Equally, we have no definitive answers as to why patients experiencing poor control of emesis after receiving one antiemetic should respond well to another, particularly to drugs of the same class.

In this short review, we have suggested reasons why some 5-HT_3-receptor antagonists may be effective in patients refractory to other antiemetic treatment, including other 5-HT_3-receptor antagonists. We speculate that granisetron may be effective where ondansetron fails, due in part to the nature of its hepatic metabolism–it is the only 5-HT_3-receptor antagonist not metabolized via the genetically polymorphic enzyme CYP2D6, its long duration of action and the use of a sub-optimal dose of the comparator 5-HT_3-receptor antagonist may further contribute to these findings. Additionally, antagonism of 5-HT release from enterochromaffin cells and genetic differences in the SERT may add to the possible reasons for improved antiemetic response to one agent over another. Further studies investigating the efficacy of antiemetic agents in patients refractory to previous other antiemetic therapy are needed.

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