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Review paper

Clinical experience with intravenous granisetron

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This review discusses the development and use of 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonists, especially granisetron, for the treatment of chemotherapy-induced emesis. Following recent evidence suggesting that high-dose chemotherapy is more effective in increasing tumor response rate and median survival time, more effective antiemetic control is essential. Granisetron, a new 5-HT$_3$, is approximately 400 times more potent than metoclopramide and, unlike metoclopramide, does not produce extrapyramidal side effects. Granisetron has been shown to be effective as a single prophylactic dose, over 5 days and in patients receiving repeated cycles of chemotherapy. Patients with nausea and vomiting within the first 24 h after chemotherapy are more likely to experience delayed symptoms; however, episodes of breakthrough nausea and vomiting can be controlled by intervention with one, and in some cases more, doses of granisetron. The development of granisetron represents an important advance in the control of chemotherapy induced emesis.

Key words: Antiemetic, granisetron, nausea, review, vomiting.

Introduction

Nausea and vomiting continue to be critical problems in cancer patients receiving emetogenic therapy. For example, prophylaxis with high-dose metoclopramide [the most efficacious antiemetic prior to the development of the selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists] is only partially effective. Approximately 60% of cisplatin-treated patients experience breakthrough symptoms of varying degrees of severity after prophylaxis with metoclopramide.[1] Severe medical consequences can include dehydration, electrolyte imbalance, metabolic alkalosis, malnutrition, vitamin deficiencies, esophageal ruptures and bone fractures. Although these can be accurately diagnosed and successfully treated,[2] there are many patients whose quality of life is compromised by persistent nausea and anticipatory symptoms. Antiemetic control is essential, as up to 30% of patients have been reported to refuse chemotherapy and up to 20% more will delay treatment, or miss clinic appointments, because of nausea and vomiting.[3] The resulting lack of compliance with chemotherapy could have serious implications with regard to the success of cancer treatment, as there is evidence to suggest that when high doses or concentrations of antitumor therapy are achieved a substantial increase in tumor response rate occurs[4] and, in some types of cancer, relative dose intensity of chemotherapy has been correlated significantly with median survival time.[5]

The advent of the 5-HT$_3$ receptor antagonists

Currently available antiemetic therapies are only partially effective especially against highly emetogenic chemotherapy regimens such as cisplatin. The most effective of these conventional antiemetics are the dopamine D_2 receptor antagonists, such as metoclopramide, but dopamine antagonism does produce problems such as extrapyramidal symptoms (dyskinesia, agitation, akathisia). Multidrug combination regimens are employed, which include benzodiazepines and antihistamines in order to ameliorate side-effects, e.g. metoclopramide/dexamethasone/lorazepam/diphenhydramine. However, agents that are used in combination can also produce their own burden of problems such as sedation (benzodiazepines), generalized swelling, lethargy and pruritus (corticosteroids). In addition, combination regimens may be cumbersome and inconvenient to administer, requiring prolonged infusions or repeated injections.

The role of the 5-HT$_3$ receptor subtype in emesis first became apparent from the introduction into clinical practice of very high doses of metoclopramide (up to 10 mg/kg/day) as a more effective treatment for cytostatic-induced emesis.[6] This indicated that mechanisms other than dopamine recep-

tor blockade could be operating in the prevention of emesis. Bianchi *et al.*[7] and Fontaine and Reuse[8] had previously demonstrated that high concentrations of metoclopramide inhibited the effects of 5-HT on receptors in gut neurones *in vitro*. These two lines of research led to the development of the hypothesis that high doses of metoclopramide *in vivo* would act to prevent cytostatic-induced emesis by blockade of the M (5-HT_3) receptor site on vagal afferent neurones in the gut and centrally at the area postrema, the site of the chemoreceptor trigger zone (CTZ). Subsequent studies in the conscious ferret model were able to substantiate this hypothesis, with the use of a selective 5-HT_3 receptor antagonist that was free from dopamine receptor antagonist activity.[9]

The new 5-HT_3 receptor antagonists are an example of a series of compounds with a relatively similar spectrum of activity. Granisetron is a particularly effective member of this class because it is approximately 400 times more potent than metoclopramide as a 5-HT_3 receptor antagonist.[10] In addition, granisetron is very selective for the 5-HT_3 receptor and does not antagonize dopamine D_2 receptors[11] and consequently it does not produce the extrapyramidal side effects that are associated with metoclopramide.[12] Furthermore, unlike some other 5-HT_3 receptor antagonists, there is no affinity for 5-HT_4 receptors agonism of which may actually induce vomiting.[13] Studies in patients receiving cisplatin and non-cisplatin chemotherapy showed granisetron to be an effective antiemetic that was well tolerated with an excellent side effect profile when given: as a single prophylactic dose;[5] over 5 days;[14] and in repeated cycles of chemotherapy.[15] In dose-ranging studies an increase in granisetron dose from 40 to 160 μg/kg had no significant effect on efficacy or incidence of adverse events, an indication of its wide therapeutic margin.[16,17] In the majority of subsequent granisetron studies the patients' response to therapy was assessed according to the schedule detailed in Table 1.

Table 1. Antiemetic efficacy criteria for granisetron studies

Complete responder	Patients who experienced no emetic episodes and had no nausea, or only mild nausea, in the 24 h after the initial administration of antiemetic therapy.
Major responder	Patients who experienced just one emetic episode, or if no vomiting, recorded moderate to severe nausea in the first 24 h.
Minor responder	Patients who had two to four emetic episodes in the first 24 h regardless of nausea rating.
Failure	Patients who had more than four emetic episodes in the first 24 h, regardless of nausea rating.

An emetic episode is equivalent to one vomit or one retch. The complete responder and major responder categories were combined to define the major efficacy category.

Granisetron as a prophylactic and intervention agent

Prevention

A randomized, double-blind, dose-finding study[16] with i.v. granisetron in 296 patients undergoing high-dose cisplatin chemotherapy, showed that at doses of 40 and 160 μg/kg i.v. granisetron afforded a high level of protection against nausea and vomiting over 24 h, with 57 and 60% of patients being complete responders, respectively (Table 2). There were no differences between the dosage groups in the survival time to the first occurrence of nausea or the first vomit. In the 40 and 160 μg/kg treatment groups 42 and 44%, respectively, who had a single dose of granisetron on the day of chemotherapy remained complete responders at the end of the 7-day follow-up period. This indicates the importance of the control of emesis on the first day.

The efficacy of granisetron against cisplatin-induced emesis has also been confirmed in comparative studies with a combination of high-dose metoclopramide and dexamethasone.[18,19]

Overall, the granisetron group had a higher proportion of major responders which led to figures for patients in the major efficacy category of 83% with granisetron and 77% with metoclopramide plus dexamethasone. In addition, the percentage of failures was higher in the metoclopramide plus dexamethasone (10%) group in comparison with those who received granisetron prophylaxis (5%). Figure 1 indicates the efficacy of antiemetic prophylaxis, stratified by dose of cisplatin, in the study conducted by Chevallier *et al.*[19]

In patients receiving various moderately emetogenic chemotherapy regimens the dose–response relationship for granisetron has also been investigated in a randomized, double-blind study.[17] Both dose levels produced a high degree of complete response with 75% of those receiving 40 μg/kg and 81% of those receiving 160 μg/kg being complete responders in the first 24 h, and little difference in

Table 2. Antiemetic efficacy of granisetron prophylaxis

Reference	Chemotherapy regimen (No. of patients)	Antiemetic (dosage)	24 h efficacy (%)		No. (%) of patients requiring additional antiemetics
			complete response	failure	
Soukop *et al.*[16]	high-dose cisplatin	G 40 μg/kg	57	9	55 (37)
	(n = 296)	G 160 μg/kg	60	8	48 (33)
Chevallier *et al.*[19]	high-dose cisplatin	G 40 μg/kg	70	7	30 (20)
	(n = 281)	MET/DEX	67	14	not known
Cupissol *et al.*[26]	high-dose cisplatin	G 40 μg/kg	93	7	1 (7)
	(n = 28)	P	7	93	13 (93)
			$p < 0.001$		
Smith *et al.*[17]	moderately emetogenic	G 40 μg/kg	75	—	49 (20)
	chemotherapy	G 160 μg/kg	81	—	39 (15)
	(n = 504)				
Marty *et al.*[20]	moderately emetogenic	G 40 μg/kg	68	—	25 (19)
	chemotherapy	CPZ/DEX	47	—	not known
	(n = 266)				
			$p < 0.001$		

Abbreviations: CPZ, chlorpromazine; DEX, dexamethasone; G, granisetron; MET, metoclopramide; P, placebo.

efficacy was observed between patients receiving different chemotherapy regimens (Figure 2). However, in a comparison with a standard combination antiemetic regimen (chlorpromazine plus dexamethasone)[20] prophylaxis with granisetron produced a statistically significantly greater complete response rate (68 versus 47%; $p < 0.001$) which was well maintained during the period of the study (Table 2).

Intervention

Investigations in the conscious ferret model of cisplatin-induced emesis indicated that intervention with granisetron could rapidly (5–30 s) terminate vomiting in mid-sequence with a single i.v. dose[21] and led to further clinical studies of intervention efficacy.[11]

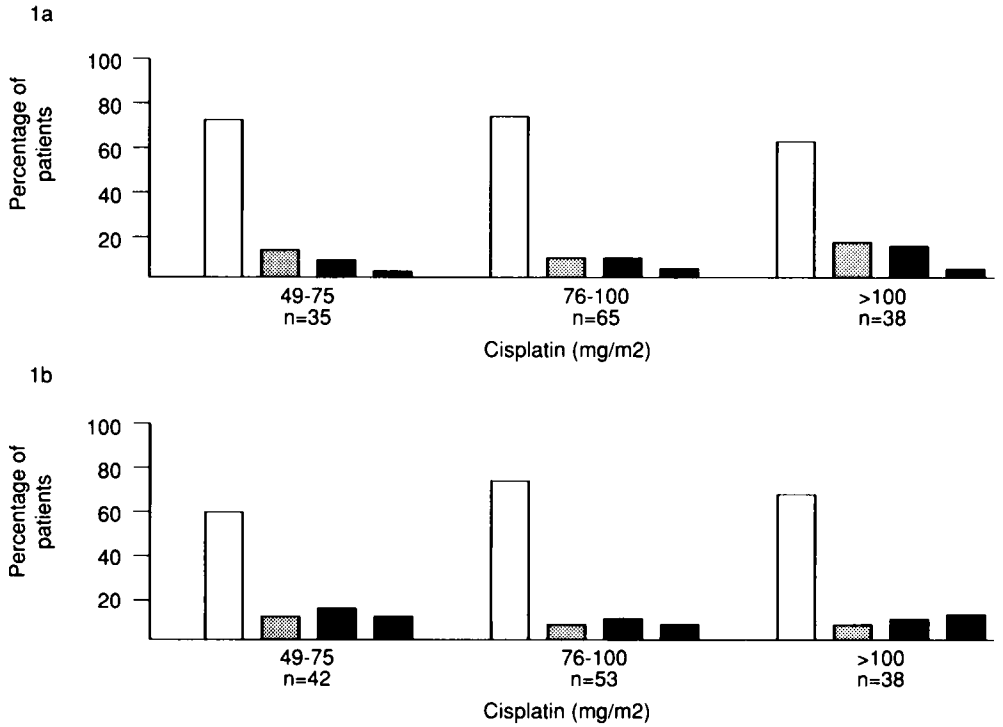

Figure 1. 24 h antiemetic efficacy compared with dose of cisplatin in patients receiving antiemetic prophylaxis with granisetron (1a) or metoclopramide plus dexamethasone (1b) (from Chevallier *et al.*,[19] with permission). □, complete; ▨, major; ▩, minor; ■, failure.

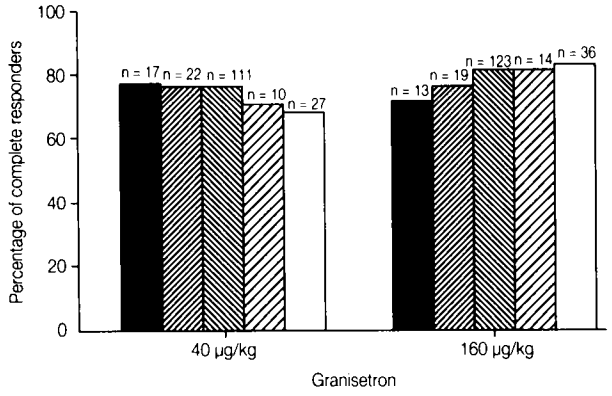

Figure 2. Major efficacy responses for different moderately emetogenic cytostatic regimens in patients receiving antiemetic prophylaxis with granisetron (40 or 160 µg/kg) (from Smith *et al.*,[17] with permission). ■, carboplatin; ▩, cisplatin; ▩, cyclophosphamide; ▨, dacarbazine; □, others.

Patients who experience no emesis in the initial 24 h following cisplatin administration have been shown to be less likely to experience delayed symptoms.[22–24] This is confirmed using data from one study in 110 evaluable cisplatin-treated patients, where delayed emesis was reported by 26.4% of patients that did not vomit in the first 24 h and by 53.1% that did vomit ($p < 0.014$).[24] This indicates that an improvement in the control of emesis on the day of chemotherapy may lead to a lower incidence of delayed nausea and vomiting. In order to obtain the best possible control of acute emesis, intervention doses in patients that breakthrough in the first 24 h has been given.

The protocols of the granisetron studies outlined in Table 2 permitted the use of further infusions of granisetron for the treatment of breakthrough vomiting or moderate to severe nausea. Thus, during the first 24 h from administration of chemotherapy the total dose of granisetron, administered for both prophylaxis and intervention, ranged from 40 to 240 µg/kg. Any further treatment required was provided by standard antiemetics.

Breakthrough nausea and vomiting in the first 24 h after chemotherapy followed different patterns in the different antiemetic groups. In a preliminary analysis of the data, Chevallier[18] found that in patients who received metoclopramide/dexamethasone, 50% of the cases of vomiting, 58% of the cases of nausea and 55% of the reports of worsened appetite, occurred in the first 6 h after cisplatin administration. However, the pattern in the granisetron group was more linear and it was 12 h before 50% of the cases of nausea, vomiting or worsened appetite had occurred. In a similar preliminary analysis, Marty[25] also observed that in the first 6 h, 13% of the chlorpromazine/dexamethasone group and 7% of the granisetron group had vomited, a cumulative percentage ratio in favor of granisetron of 0.53, which was maintained to the 18 h assessment, followed by a ratio of 0.58 to the end of the first 24 h. A similar, but less pronounced trend in favor of granisetron treatment was evident in the data for the onset of nausea.

The numbers and percentages of granisetron pretreated patients who required additional intervention treatment with the antiemetic in the first 24 h are detailed in Table 2. A single additional dose of granisetron resolved or improved breakthrough symptoms in the majority of those patients who required further treatment with the antiemetic. There was a slight trend towards a higher response rate to the first additional dose in the patients who received moderately emetogenic chemotherapy,[17,20] as opposed to highly emetogenic high-dose cisplatin therapy (Figure 3).[16,19]

The efficacy of granisetron as an intervention agent was also specifically assessed in comparison with placebo in the study conducted by Cupissol[26] in patients who received high-dose cisplatin chemotherapy (Table 2). In the placebo pretreated group, 13 of 14 patients (93%) needed intervention with granisetron for breakthrough nausea and vomiting. All of these patients showed resolution or improvement of symptoms with a single intervention dose. However, five of these patients received a second dose and one received a third dose within 24 h in order to achieve resolution of symptoms. In these cases, administration of granisetron produced a response within a few minutes of infusion.

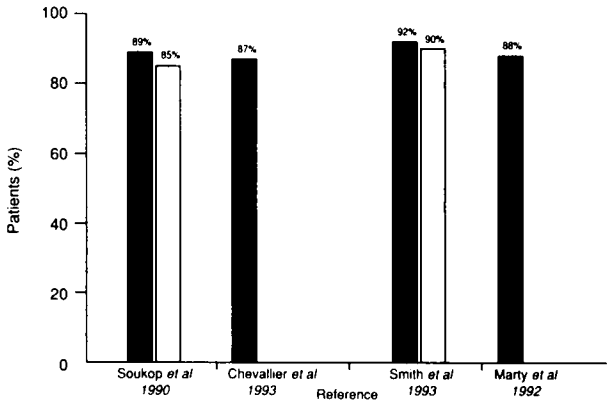

Figure 3. Percentage of patients with breakthrough symptoms resolved or improved after a single additional dose of granisetron following antiemetic prophylaxis with granisetron 40 µg/kg (■) or granisetron 160 µg/kg (□).

Comparative data with other 5-HT_3 antagonists

Recently three studies have been reported which compare granisetron with other 5-HT_3 receptor antagonists.

In the first, 175 chemotherapy naive patients scheduled to receive moderately emetogenic chemotherapy were randomized to receive either intravenous ondansetron 8 mg followed by 8 mg orally every 8 h for 3 days, or prophylactic intravenous granisetron 3 mg.[27] One hundred and fifty patients were crossed to receive the alternative regimen during their second chemotherapy course.

No difference in efficacy was observed between the two drugs, with approximately 75% of patients experiencing no vomiting on day 1. Adverse events with both antiemetic treatments were mild and similar across both groups, with constipation, headache and diarrhea being the most common. There was no difference in patient preference for one drug over another—39% preferred granisetron, 34% ondansetron and 27% had no preference.

In a second cross-over study, Noble *et al.* compared granisetron with ondansetron in patients scheduled to receive 5 day fractionated chemotherapy.[28] Patients were randomized to receive either prophylactic intravenous granisetron 3 mg each day or ondansetron 8 mg given as three intravenous infusions every 8 h, each day. A total of 359 patients were randomized and 309 completed the cross-over. The efficacy of granisetron and ondansetron were comparable over the first 24 h of cycle 1 and over the 5 day period. Approximately 90% of patients in both groups were complete responders (no vomiting and no or only mild nausea). Over the 5 day period complete response was achieved in approximately 40% of patients in both groups. Interestingly, a significant difference was observed in patient preference in favor of granisetron. Of those patients who expressed a preference, 34% preferred granisetron and 26% preferred ondansetron ($p < 0.05$). There were no differences between the adverse event profiles of the two drugs, with headache and constipation the most frequently reported.

Jantunen *et al.* compared single-dose granisetron (3 mg), ondansetron (8 mg) and tropisetron (5 mg) in a randomized prospective cross-over study.[29] One hundred and thirty patients receiving moderately emetogenic chemotherapy were evaluable. During the initial 24 h period complete control of vomiting was achieved in 80% of patients receiving granisetron, compared with 75% receiving tropisetron and 69% receiving ondansetron ($p < 0.05$ granisetron versus ondansetron). When asked, 34% patients expressed a preference for granisetron, 17% for ondansetron and 15% for tropisetron ($p < 0.05$ granisetron versus ondansetron).

Conclusions

The pattern of emesis produced by cytostatic drugs is variable and may persist for several days. Effective antiemetic control requires the use of an antiemetic with peak activity over with the worst period of nausea and vomiting for the particular cytostatic drug involved.[26] Episodes of breakthrough nausea and vomiting can be quickly controlled by intervention with a single 40 μg/kg dose of granisetron although one or two further infusions may be necessary for complete resolution in some patients.[16,17,19,26]

The advantages of granisetron as a prophylactic with an excellent safety profile are of paramount importance, especially in relation to the conventional (non-5-HT_3 receptor antagonist) antiemetic combinations. The latter may involve the use of multidrug regimens which pose an increased risk of adverse reactions or drug interactions[12] and whose complicated dosage schedules compare unfavorably with the 5 min period of infusion needed to administer granisetron.

Available comparative data show granisetron to be equivalent or superior to ondansetron, with a similar safety profile. Patient preference data were in favor of granisetron, which may indicate differences between 5-HT_3 receptor antagonists not detected by gross measurement of nausea and vomiting.

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