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Clinical Studies with Granisetron, a new 5-HT_3 Receptor Antagonist for the Treatment of Cancer Chemotherapy-induced Emesis

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Granisetron (BRL 43694A) is a novel, selective 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist developed for the prophylaxis and treatment of cytostatic drug-induced emesis. After a brief review of the preclinical evaluation of granisetron the clinical findings with this novel compound are summarised. From the data of large randomised trials one can conclude that granisetron is an active antiemetic, both as a prophylactic and an intervention agent, to an extent which is superior or at least equal to the best available antiemetic combination regimens, having a major efficacy ranging from 74 to 92%. Granisetron may be given as a single, 5-min infusion before chemotherapy and is thus more convenient to administer than many antiemetic regimens. The adverse event profile of granisetron is favourable with a wide therapeutic margin. The only consistent side-effects attributable to granisetron are headache in about 14% of the patients and constipation in about 4% of the patients. Headache induced by granisetron was generally mild and resolved spontaneously or was promptly relieved with standard analgesics. No extrapyramidal side-effects were observed with granisetron.
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NAUSEA AND VOMITING are the major dose-limiting side-effects for a number of cytostatic drugs such as cisplatin, doxorubicin and nitrogen mustard. With the widespread use of these and other cytostatic agents in the mid-1970s emesis was recognised as a critical problem in cancer chemotherapy and led Whitehead in 1975 to make "a plea to all cooperative chemotherapeutic groups to undertake a search for effective antiemetic therapy as an additional and integral part of current and future chemotherapeutic trials, testing one and another agent, alone and in combinations, to determine means to overcome gastrointestinal toxicity. Success would permit patients to complete courses of chemotherapy and would improve substantially the quality of life during such therapy" [1]. The relevance of this statement is underlined by the fact, that patients perceive vomiting and nausea as the most distressing treatment-related effects of cancer chemotherapy [2].

In the early 1980s high-dose metoclopramide was established as a very effective therapy of chemotherapy-induced nausea and vomiting [3]. The antiemetic effects of high-dose metoclopramide were believed to reflect its dopamine D2 receptor blocking activity although very high doses are required for efficacy and despite the fact that a variety of other dopamine receptor antagonists are generally less effective.

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Researchers were aware of reports that high concentrations of metoclopramide *in vitro* could inhibit the effects of 5-hydroxytryptamine on receptors located on gut neurones, suggesting that the antiemetic activity of high-dose metoclopramide might be related to the antagonism of 5-hydroxytryptamine-3 (5-HT_3) receptors at peripheral and possibly at central sites [4]. In 1986 Miner and Sanger investigated the antiemetic potential of compounds which share the 5-HT_3 receptor antagonist properties of metoclopramide but which lack any effect at dopamine receptors. They showed that a 5-HT_3 receptor antagonist, which was free from dopamine receptor antagonist properties, was like metoclopramide an effective suppressant of vomiting induced by cisplatin in the ferret [5]. These observations led to the development of a novel, selective 5-HT_3 receptor antagonist {endo-*N*-[9-methyl- 9-azabicyclo(3.3.1)non-3-yl]-1-methyl-1H-indazole-3-carboxamide hydrochloride; BRL 43694A; Granisetron}.

PHARMACOLOGICAL PROPERTIES OF GRANISETRON

Granisetron is highly effective in the prevention and therapy of cisplatin-induced vomiting in the conscious ferret. Emesis cannot only be prevented by prophylactic treatment with granisetron, but it can also be abruptly terminated in mid-sequence within 5–30 s after a single intravenous dose of the drug. Granisetron is also effective in preventing emesis induced by other cytostatic regimens or by whole body X-irradiation [6]. From these and other data one can conclude that:

—granisetron is a potent, competitive 5-HT_3 receptor antagonist *in vitro* and *in vivo*

—granisetron is highly selective for 5-HT_3 receptors and shows very low affinity for other receptors

—low doses of granisetron prevent the severe emesis and retching which are evoked in the conscious ferret by antineoplastic cytotoxic drugs such as cisplatin, cyclophosphamide, doxorubicin or by whole body X-irradiation
—vomiting evoked by these stimuli can be quickly stopped in mid-sequence by a single intravenous dose of granisetron
—no side-effects were apparent following antiemetic doses of granisetron.

When antiemetics are used in patients receiving cancer chemotherapy, the question of whether these drugs interfere with the antitumour activity of the cytostatic agents is important. Goddard and co-workers [7] investigated the interaction between cisplatin and granisetron. The results observed suggest that granisetron might even increase the antitumour activity of the cytostatic, as granisetron retained cisplatin within the tumour cells.

As will be discussed later, granisetron is a well tolerated and safe drug in humans. During the preclinical evaluation granisetron was subjected to routine toxicology including 2-year carcinogenicity studies in Sprague–Dawley rats and CD-1 mice [8]. An unexpected increased incidence of hepatocellular neoplasia (adenoma and carcinoma) in male and female mice which were given 50 mg/kg/day and males given 5 mg/kg/day of granisetron was observed. However, no hepatocellular carcinomas were found in the low dose group (1 mg/kg/day). These data show that granisetron administered at high doses daily for 2 years is hepatocarcinogenic in animals with a clear no-effect dose at 1 mg/kg, a dose level 25 times greater than the most common dose used in clinical studies (40 μg/kg). A 12-month toxicity study in the dog showed no evidence of any histopathological changes related to treatment. In summary, the induction of increased numbers of tumours in rodent livers, with no evidence for a genotoxic mechanism and a clear no-effect level of 1 mg/kg/day (25 times the normal human dose) after lifetime exposure, should not be considered to represent a hazard for the short-term, intermittent use of granisetron as an antiemetic drug.

GRANISETRON IN HUMAN VOLUNTEERS

In 1987 studies in human male volunteers, with doses of granisetron up to 300 μg/kg administered by a 30-min intravenous infusion, demonstrated good tolerance with no apparent effects on the CNS [9]. The only consistent complaint which was not observed with placebo, was of constipation. Granisetron was found to have a large volume of distribution. It was rapidly eliminated (mean half life ≈5 h) being cleared largely through non-renal mechanisms. Kinetics were linear over the clinical dose range. There were wide intersubject differences in kinetics, with a more than 10-fold variability in terminal phase half-life and total plasma clearance [10].

In these studies the duration of activity was assessed in volunteers by measuring the degree of inhibition of the axon-reflex flare induced by intradermal injection of 5-HT. The flare area was decreased after active treatment when compared with placebo. The decrease was evident at the end of the infusion and was still present 24 h later. Thus, despite rapid elimination of the compound from the plasma there was evidence of pharmacodynamic activity for up to 24 h after a single dose of 40 μg/kg [11].

In summary these studies showed that granisetron in dosages up to 300 μg/kg was well tolerated by healthy volunteers. In dosages to be used clinically there was no detectable CNS effect of granisetron. In these studies there was evidence of a prolonged pharmacodynamic effect.

GRANISETRON IN TUMOUR PATIENTS RECEIVING EMETOGENIC CANCER CHEMOTHERAPY

With this information from human volunteers several academic centres initiated pilot studies in cancer patients.

Pilot studies of granisetron

At the University of Bern, Switzerland, one of the early pilot trials was initiated in August 1987; within 12 months 11 female and 18 male ambulatory tumour patients having a median age of 38 years (24–65 years) were treated with granisetron administered as a 30-min infusion 1 h after the application of the cytostatics. The first 7 patients were treated with a dose of 40 μg/kg body weight. Thereafter, we increased the dose to 100 μg/kg (13 patients). The last 9 patients received an initial dose of 40 μg/kg with a provision for an additional two doses of 40 μg/kg over the next 24 h, provided that the patients suffered from severe nausea or from vomiting. 17 patients received cisplatin $\geqslant 50$ mg/m^2 as their first course of chemotherapy; 12 patients were established vomiters (these patients had experienced >5 vomiting episodes during a previous course of chemotherapy despite conventional antiemetic treatment with a combination of high-dose metoclopramide, methylprednisolone and flunitrazepam). 14 patients (48%) had no vomiting episodes; 7 patients (24%) had 1–2 episodes; 6 patients (21%) had 3–5 episodes; and only 2 patients suffered from severe vomiting (8 and 11 episodes, respectively, over the 24 h following the administration of the chemotherapy). The antiemetic efficacy was maintained during subsequent courses. No consistent adverse events were attributable in this small series to granisetron [12, 13].

This and other very encouraging pilot studies led to the formation of the Granisetron Study Group in 1988, a collaborative effort of oncologists in seven countries to carry out the definitive clinical trials with granisetron (see appendix for list of participants). Hereafter, some of the findings of this group will be highlighted. Throughout these trials the following definitions were used:

Complete responder	— no nausea or vomiting or only mild nausea in the 24 h after starting cytostatic therapy
Major responder	— single vomiting episode in the 24 h after starting cytostatic therapy or no vomiting, but moderate to severe nausea
Minor responder	— 2–4 vomiting episodes in the 24 h after starting chemotherapy
Failures	— >4 vomiting episodes in the 24 h after starting chemotherapy
Major efficacy	— complete and major responders

In all these trials the patients were treated as inpatients during the first 24 h. Subjective assessment of nausea and appetite was made every 6 h and the number of vomiting episodes was recorded for each 6-h period. After discharge the patients received a diary card on which they recorded nausea and vomiting for the following 6 days.

Granisetron vs. placebo

Cupissol and co-workers carried out a double-blind, placebo-controlled study in 28 chemotherapy-naive patients receiving cisplatin at a mean dose in excess of 80 mg/m^2 with 4 patients in each group receiving less than 80 mg/m^2 [14]. Cisplatin doses were administered over a maximum period of 6 h. Patients were randomised into two groups receiving either granisetron (40 μg/kg) or placebo. Patients in both groups who experienced symptoms of vomiting and nausea were given up to a further three 40 μg/kg doses of granisetron on an open-label basis, allowing the assessment of granisetron as an intervention antiemetic in the placebo group. As a result of the randomised allocation, 4 more female patients were entered into the placebo treatment group than into the granisetron treatment group. Patients in the granisetron group received a mean cisplatin dose of 86.4 mg/m^2, those in the placebo group a mean dose of 80.5 mg/m^2. Following granisetron 13 of 14 patients (93%) had no vomiting or nausea in the first 24 h, a significant difference compared with the 1 patient in the placebo group who remained free of vomiting and had only mild nausea in the same period ($P<0.001$). As a single intervention agent, granisetron achieved control or improvement of existing symptoms in the remaining patients of the placebo group. The 1 patient in the granisetron group, who experienced vomiting, did so after 16 h, whereas in the placebo group 12/14 patients started vomiting between 4 and 8 h after the chemotherapy. This trial definitely established granisetron as a very active antiemetic drug compared with placebo in patients receiving chemotherapy with high doses of cisplatin. Furthermore the study demonstrated the potential of granisetron as a single agent for abolishing established vomiting.

Dose-finding studies of granisetron

After having proven the impressive antiemetic activity of granisetron two double-blind dose finding studies were carried out in patients receiving high-dose cisplatin (≥50 mg/m^2) or other moderately emetogenic chemotherapies comparing two dose levels of granisetron (40 and 160 μg/kg).

In the first double-blind, randomised multicentre study 335 chemotherapy-naive patients undergoing high-dose cisplatin chemotherapy (≥50 mg/m^2) were given an initial dose of granisetron over 30 min finishing 5 min before the start of the cisplatin chemotherapy [15]. 170 patients were given an initial dose of 40 μg/kg and 165 patients a dose of 160 μg/kg. Up to two additional doses of open label intravenous granisetron (40 μg/kg) were allowed during the first 24 h for patients who experienced breakthrough nausea and vomiting in both groups. This meant that patients could receive between 40 and 240 μg/kg granisetron in 24 h. The cisplatin infusions lasted from 20 min to 10 h, with only 17 patients receiving the infusion for more than 6 h. No difference in efficacy or safety between the two doses of granisetron was established. 57 and 59% of the patients treated at the low and high dose level, respectively, experienced no vomiting and no more than mild nausea (see Table 1). When patients receiving cisplatin in a dose ≥100 mg/m^2 are analysed separately, similar results were observed (Table 2). The adverse event profile was similar for both the 40 and the 160 μg/kg groups. Further details of the safety profile of granisetron will be discussed below.

In summary this trial showed granisetron in the dose range of 40–240 μg/kg to be well tolerated in this group of patients and to be a very effective antiemetic. There were no clinically significant differences observed in the efficacy or safety profile between those patients receiving an initial dose of either 40 μg/kg or 160 μg/kg.

Table 1. Results of a double-blind, randomised, dose-finding study in 335 chemotherapy-naive patients undergoing high-dose cisplatin chemotherapy (≥50 mg/m^2)

	Treatment group	
	40 μg/kg ($n=170$)	160 μg/kg ($n=165$)
Complete responders	57%	59%
Major responders	17%	15%
Minor responders	18%	18%
Failures	8%	8%

Table 2. Subgroup analysis of patients undergoing high-dose cisplatin chemotherapy (≥100 mg/m^2) in a double-blind, randomised, dose-finding study

	Treatment group	
	40 μg/kg ($n=35$)	160 μg/kg ($n=38$)
Complete responders	42%	34%
Major responders	20%	24%
Minor responders	29%	32%
Failures	9%	10%

A second trial with an identical design was conducted in 504 patients undergoing moderately emetogenic therapy with a range of standard cytostatic treatments [16]. The minimum cytostatic regimen(s) for eligibility to enter into the study were:

—carboplatin ≥ 300 mg/m^2
—cisplatin ≥ 20–≤50 mg/m^2
—cytophosphamide ≥ 600 mg/m^2 (in combination therapy)
—dacarbazine ≥ 350–<500 mg/m^2
—doxorubicin ≥ 40 mg/m^2 (single agent)
—doxorubicin ≥ 25 mg/m^2 (in combination therapy)
—epirubicin ≥ 75 mg/m^2 (single agent)
—epirubicin ≥ 50 mg/m^2 (in combination therapy)
—nitrogen-mustard ≥ 6 mg/m^2

Other cytostatic drugs were allowed concurrently using the usual dosing schedules as long as they were not routinely covered with an antiemetic drug. All patients were naive to cytotoxic chemotherapy. After 24 h the results as shown in Table 3 were observed. When the results were analysed by the primary emetogenic drug, no differences in complete

Table 3. Results of a double-blind, randomised, dose-finding study in 504 patients undergoing moderately emetogenic therapy with a range of standard cytostatic treatments

	Treatment group	
	40 μg/kg ($n=251$)	160 μg/kg ($n=253$)
Complete responders	75%	81%
Major responders	16%	10%
Minor responders	6%	6%
Failures	3%	3%

Table 4. Subgroup analysis according to the emetic stimulus in a double-blind, randomised, dose-finding study in 504 patients undergoing moderately emetogenic therapy

	Treatment group	
	40 μg/kg ($n=251$)	160 μg/kg ($n=253$)
Cyclophosphamide	76%	82%
Cisplatin	76%	76%
Carboplatin	77%	72%
Dacarbazine	71%	82%
Other	68%	83%

protection were seen between the two treatment groups (see Table 4). The adverse event profile was similar in both groups and will be discussed in further detail later.

In conclusion, this trial showed that granisetron is an effective antiemetic therapy in these types of chemotherapy. The efficacy of granisetron did not vary according to the dose level or the type of cytostatic chemotherapy in use.

Comparative studies of granisetron with standard antiemetic regimens

In two protocols the efficacy and safety of granisetron were compared with standard antiemetic therapy.

In the first protocol granisetron was compared to high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin (≥ 50 mg/m^2) [17]. In this single-blind study granisetron 40 μg/kg was administered as a 5-min infusion completed 5 min before the start of the cisplatin administration, with two additional doses of granisetron allowed to control subsequent nausea and vomiting. Patients given standard antiemetic therapy received 12 mg dexamethasone followed immediately by a loading dose of 3 mg/kg metoclopramide administered as a 30-min infusion (range 25–70 min). This procedure was completed 5 min before the start of the cisplatin administration. A maintenance dose of 4 mg/kg of metoclopramide was then infused over 8 h. Standard antiemetics were used to treat breakthrough nausea and vomiting in this group. The choice of medication was left to the physician in charge, though granisetron was not permitted. The infusion time for cisplatin ranged from 15 min to 8 h, with only 3 patients receiving the infusion for longer than 6 h.

281 patients (183 males, 98 females) were randomly allocated to receive either granisetron ($n=143$) or the standard antiemetic regimen (high-dose metoclopramide plus dexamethasone; $n=138$). All but 4 patients were naive to chemotherapy. After 24 h the results detailed in Table 5 were observed. 83% of the granisetron-treated patients and 77% of the patients receiving standard antiemetic therapy experienced major protection from gastrointestinal side-effects of the cisplatin chemotherapy. When patients receiving cisplatin ≥ 100 mg/m^2 were analysed separately, similar results were observed (Table 6).

Table 5. Results of a prospective, randomised study comparing granisetron with high-dose metoclopramide plus dexamethasone in 281 patients receiving high-dose cisplatin (≥ 50 mg/m^2)

	Treatment group	
	Granisetron ($n=143$)	Metoclopramide + dexamethasone ($n=138$)
Complete responders	70%	68%
Major responders	13%	9%
Minor responders	12%	13%
Failures	5%	10%

Table 6. Subgroup analysis of patients undergoing high-dose cisplatin chemotherapy (≥ 100 mg/m^2) in a prospective, randomised study comparing granisetron with high-dose metoclopramide plus dexamethasone

	Treatment group	
	Granisetron ($n=38$)	Metoclopramide + dexamethasone ($n=38$)
Complete responders	63%	68%
Major responders	18%	8%
Minor responders	16%	11%
Failures	3%	13%

Adverse events were recorded by 33 patients (23%) in the granisetron treatment group and 45 patients (33%) in the comparator group. Further details will be discussed below. However, it should be noted here that 15 patients (10.8%) treated with high-dose metoclopramide plus dexamethasone experienced extrapyramidal reactions compared with none in the granisetron group.

In conclusion, this trial established granisetron as an effective antiemetic at least as effective as the commonly used standard antiemetic regimen of high-dose metoclopramide plus dexamethasone. Granisetron did not produce the potentially serious extrapyramidal reactions seen with high-dose metoclopramide.

In a further trial in 243 patients treated with moderately emetogenic chemotherapy granisetron was compared with a combination of chlorpromazine and dexamethasone [18]. The minimum cytostatic regimen(s) for eligibility to enter into the study were:

—carboplatin ≥ 300 mg/m^2
—cisplatin ≥ 20–50 mg/m^2
—cyclophosphamide ≥ 600 mg/m^2 (in combination therapy)
—dacarbazine ≥ 350–<500 mg/m^2
—doxorubicin ≥ 40 mg/m^2 (single agent)
—doxorubicin ≥ 25 mg/m^2 (in combination therapy)
—epirubicin ≥ 75 mg/m^2 (single agent)
—epirubicin ≥ 50 mg/m^2 (in combination therapy)
—nitrogen-mustard ≥ 6 mg/m^2

Other cytostatic drugs were allowed concurrently using the usual dosing schedules as long as they were not routinely covered with an antiemetic drug. Granisetron was administered in a dose of 40 μg/kg (as a short infusion over a mean time of 7.2 min) to be completed 5 min prior to the application of the chemotherapy. Patients in the control arm received dexamethasone 12 mg infused over 30 min prior to the chemotherapy together with 25 mg of chlorpromazine injected intramuscularly or intravenously prior to the chemotherapy followed by oral chlorpromazine at 4–6 hourly intervals to a maximum dose of 200 mg within the first 24 h of the study.

243 patients were randomly allocated to receive either granisetron ($n=123$) or the standard antiemetic regimen (dexamethasone plus chlorpromazine; $n=120$). All but 12 patients were naive to chemotherapy. The patients received the types

Table 7. Chemotherapeutic regimens used in a prospective, randomised study in 243 patients treated with moderately emetogenic chemotherapy comparing granisetron with a combination of chlorpromazine and dexamethasone

Chemotherapy	Granisetron ($n=123$)	Dexamethasone + chlorpromazine ($n=120$)
Carboplatin	41	37
Cisplatin	19	20
Cyclophosphamide	54	51
Other regimens	9	12

Table 8. Results of a prospective, randomised study in 243 patients treated with moderately emetogenic chemotherapy comparing granisetron with a combination of chlorpromazine and dexamethasone

	Treatment group	
	Granisetron ($n=123$)	Dexamethasone + chlorpromazine ($n=120$)
Complete responders	70%	50%
Major responders	17%	14%
Minor responders	10%	17%
Failures	3%	19%

of chemotherapy detailed in Table 7. The treatment arms were well balanced for age and sex. After 24 h the results as shown in Table 8 were observed.

In the first 24 h 70% of the patients in the granisetron group were classified as complete responders compared with 49% in the conventional antiemetic group ($P \leqslant 0.001$). Of 12 patients not naive to chemotherapy, 3 of the 4 patients in the granisetron group but only 3 of the 8 patients in the comparator group were complete responders. Over the 7-day period, a total of 57 patients (50%) in the granisetron treatment group maintained a complete response, compared with 41 patients (36%) in the comparator treatment group ($P \leqslant 0.01$). Significantly fewer adverse events were reported in the granisetron group as shown in Table 9. The difference in adverse events reported and the difference in patients experiencing somnolence was statistically significant in favour of the granisetron group ($P \leqslant 0.05$ and $P \leqslant 0.053$).

This trial proved granisetron to be statistically and clinically superior to chlorpromazine plus dexamethasone in controlling nausea and vomiting associated with various emetogenic cytostatic regimens. In addition, there were significantly less adverse events reported for granisetron compared with the control arm of dexamethasone and chlorpromazine.

Table 9. Adverse events observed in a prospective, randomised study in 243 patients treated with moderately emetogenic chemotherapy comparing granisetron with a combination of chlorpromazine and dexamethasone

	Randomised group	
	Granisetron ($n=123$)	Dexamethasone + chlorpromazine ($n=120$)
Patients with one or more event(s)	28 (23%)	42 (35%)
Headache	16 (13%)	7 (5.8%)
Somnolence	1 (0.8%)	18 (15%)
Constipation	3 (2.4%)	3 (2.5%)
Diarrhoea	1 (0.8%)	3 (2.5%)
Dizziness	3 (2.4%)	4 (3.3%)

Ongoing studies of granisetron

Several further trials are currently ongoing exploring different avenues. One is a continuation study assessing the efficacy and safety of the continued use of granisetron with subsequent cycles of chemotherapy. A preliminary analysis of this ongoing trial suggests that granisetron is well tolerated after repeated administration during successive cycles of chemotherapy. The antiemetic efficacy was maintained in subsequent cycles. A Canadian multicentre trial is assessing the antiemetic efficacy and tolerance of granisetron in comparison with dexamethasone and prochlorperazine in patients receiving moderately emetogenic chemotherapy. This is a double-blind parallel group study. The preliminary analysis suggests that granisetron was more effective than dexamethasone plus prochlorperazine in preventing vomiting in the 24 h after the start of cytostatic chemotherapy. Finally, a dose finding trial with an oral form of granisetron has just been launched.

THE ADVERSE EVENTS PROFILE OF GRANISETRON

In the trials discussed above all adverse events were recorded over 7 days after the start of chemotherapy, irrespective of the cause. The adverse events observed are summarised in Table 10. Granisetron proved to be a well tolerated and safe drug. There were no differences between the two dose levels studied (40 vs. 160 μg/kg); thus increasing the dose four-fold did not change the overall safety profile. Looking at the comparator studies granisetron induced fewer adverse events than standard antiemetics. However, headache was more prevalent in granisetron-treated patients, suggesting that this is a drug-related side-effect. Headache induced by granisetron was generally mild and resolved spontaneously or was promptly relieved with standard analgesics. Constipation was more frequent in patients treated with granisetron, and diarrhoea more so in patients receiving the comparators, but the incidence and the differences were small. Somnolence was seen in significantly more patients treated with standard antiemetics compared with patients receiving granisetron. As expected, patients treated with granisetron remained free of extrapyramidal side-effects whereas 11% of the patients receiving high-dose metoclopramide plus dexamethasone suffered from potentially serious dyskinesias.

In summary, granisetron is an extremely well tolerated and safe antiemetic drug. The two most prominent side-effects of this drug are headache in about 14% of the patients and constipation in about 3% of treated individuals. Granisetron at clinical doses is devoid of effects on the cardiovascular or the central nervous system.

CONCLUSIONS

Based on the findings summarised above granisetron is a very active and safe antiemetic, both as a prophylactic and intervention agent, to an extent which is superior or at least equal to the best available antiemetic combination regimens. The degree and duration of symptom control by a single administration of granisetron will allow reductions in the hospital stay of patients receiving cancer chemotherapy and

Table 10. Adverse events most commonly reported for granisetron and standard comparator antiemetic therapies

	Dose finding in high-dose cisplatin chemotherapy		Dose finding in other moderately emetogenic chemotherapies		Comparative trial of granisetron vs. high-dose metoclopramide + dexamethasone in high-dose cisplatin		Comparative trial of granisetron vs. chlorpromazine + dexamethasone in moderately emetogenic chemotherapies		Total	
Protocol	Granisetron 40 μg/kg ($n=170$)	Granisetron 160 μg/kg ($n=165$)	Granisetron 40 μg/kg ($n=251$)	Granisetron 160 μg/kg ($n=253$)	Granisetron 40 μg/kg ($n=143$)	HD-MTC + DXM* ($n=138$)	Granisetron 40 μg/kg ($n=123$)	CLP + DXM* ($n=120$)	Granisetron all dosages ($n=1105$)	Standard antiemetics ($n=258$)
Patients with events (%)	32	30	33	31	23	33	23	35	29	34
Headache (%)	15.9	13.9	15.5	13	9.8	2.9	13	5.8	14	4
Somnolence (%)	2.4	2.4	1.2	1.6	0.7	5.1	0.8	15.0	2	10
Constipation (%)	2.9	4.2	4.0	3.6	2.1	0	2.4	2.5	3	1
Diarrhoea (%)	1.2	0.6	1.6	0.8	2.1	7.2	0.8	2.5	1	5
Dizziness (%)	2.4	1.2	3.2	0.4	0	0.7	2.4	3.3	2	2
Extrapyramidal reactions (%)	0	0	0	0	0	10.8	0	0	0	5

*HD-MTC + DXM = high-dose metoclopramide plus dexamethasone. CLP + DXM = Chlorpromazine plus dexamethasone.

treatment of more patients on an out-patient basis. Granisetron has a favourable adverse event profile, with a reassuringly wide therapeutic margin. In particular, granisetron appears to be free of serious central nervous system side-effects.

Further trials are currently ongoing investigating the efficacy of granisetron when given over several cycles of chemotherapy and evaluating the activity of an oral form of the drug. Furthermore, the potential of granisetron in combination with other antiemetics has yet to be explored. However, from the patient's point of view the introduction of granisetron into everyday clinical practice will alleviate one of the most dreaded side-effects of cancer chemotherapy.

APPENDIX
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1. Whitehead VM. Cancer treatment needs better antiemetics. *N Engl J Med* 1975, **293**, 199–200.
2. Coates A, Abraham S, Kaye SB, *et al.* On the receiving end—patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983, **19**, 203–208.
3. Gralla RJ, Itri LM, Pisko SE, *et al.* Anti-emetic efficacy of high-dose metoclopramide: randomised trial with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 1981, **305**, 905–909.
4. Bianchi C, Beani L, Crema C. Effects of metoclopramide on isolated guinea pig colon. *Eur J Pharmacol* 1970, **12**, 332–341.
5. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *Br J Pharmacol* 1986, **88**, 497.
6. Bermudez J, Boyle EA, Miner WD, *et al.* The anti-emetic potential of the 5-hydroxytryptamine-3-receptor antagonist BRL 43694. *Br J Cancer* 1988, **58**, 644–650.
7. Goddard PM, Jones M, Pollard LA, *et al.* The 5-HT_3 receptor antagonist, BRL 43694, does not compromise the efficacy of cisplatin in tumour-bearing mice. *Cancer Chemother Pharmacol* 1990, **25**, 377–379.
8. Beecham Research Laboratories, data on file, 1990.
9. Upward JW, Arnold BDC, Link C, *et al.* The clinical pharmacology of granisetron (BRL 43694A), a novel specific 5-HT_3 antagonist. *Eur J Cancer* 1990, **26**, Suppl. 1, S12–S15.
10. Zussman BD, Clarkson A, Coates PE, *et al.* The pharmacokinetic profile of BRL 43694, a novel 5-HT_3 receptor antagonist, in healthy male volunteers. *Br J Clin Pharmacol* 1988, **25**, 107P.
11. Cooper SM, Arnold BDC, Rapeport WG. Inhibition of 5-HT-induced axon-reflex flares by BRL 43694, a novel 5-HT_3 receptor antagonist. *Br J Clin Pharmacol* 1988, **25**, 106–107P.
12. Joss RA, Richner J, Brunner KW, *et al.* BRL 43694: a novel antiemetic to prevent nausea and vomiting induced by chemotherapy. *J Natl Cancer Inst* 1988, **80**,1340–1341.
13. Joss R, Rohrbach D, Buser K, *et al.* BRL 43694A–ein 5-Hydroxytryptamin-Rezeptoren-Blocker als Antiemetikum in der Zytostatika-Therapie. *Schweiz Med Wschr* 1989, **119**, 831–834.
14. Cupissol DR, Serrou B, Caubel M. The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high dose cisplatin-induced emesis. *Eur J Cancer* 1990, **26**, Suppl. 1, S23–S27.
15. Soukop M, on behalf of the Granisetron Study Group. A dose-finding study of granisetron in patients receiving high-dose cisplatin. *Eur J Cancer* 1990, **26**, Suppl. 1, S15–S19.
16. Smith IE, on behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving moderately emetogenic cytostatic chemotherapy. *Eur J Cancer* 1990, **26**, Suppl. 1, S19–S23.
17. Chevallier B, on behalf of the Granisetron Study Group. Efficacy and safety of granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. *Eur J Cancer* 1990, **26**, Suppl. 1, S33–S36.
18. Marty M, on behalf of the Granisetron Study Group. A comparative study of the use of granisetron, a selective 5-HT_3 antagonist, versus a standard anti-emetic regimen of chlorpromazine plus dexamethasone in the treatment of cytostatic-induced emesis. *Eur J Cancer* 1990, **26**, Suppl. 1, S28–S32.