Eur J Cancer, Vol. 28A, Suppl. 1, pp. S12-S16, 1992
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

A Comparison of Granisetron as a Single Agent with Conventional Combination Antiemetic Therapies in the Treatment of Cytostatic-Induced Emesis

Michel Marty
on behalf of the Granisetron Study Group

The safety and efficacy of intravenous granisetron were compared with combinations of conventional antiemetics in two single-blind, parallel-group studies which have been reported previously [1, 2]. In this review updated data from both studies is presented. In both studies granisetron (40 μg/kg) was given as a single 5-min infusion before chemotherapy with two additional doses allowed to control subsequent nausea and vomiting. All patients were naive to chemotherapy. Patients due to receive cisplatin (> 49 mg/m²) were randomly assigned to receive either granisetron alone or metoclopramide (3 mg/kg) plus dexamethasone (12 mg) given prophylactically followed by an 8-h infusion of metoclopramide (4 mg/kg). In the 24 h after the start of chemotherapy 70% of granisetron-treated patients and 67% of comparator group were complete responders. In patients due to receive moderately emetogenic chemotherapy, granisetron was compared with chlorpromazine (up to 200 mg/24 h) plus dexamethasone (12 mg). Twenty-four hour efficacy was significantly higher in the granisetron group with complete response in 68% of patients compared to 47% in the comparator group ($P < 0.001$). A subset of 40 patients in this study were crossed over to receive the alternative antiemetic on their next cycle of chemotherapy. A significant majority of patients (32/34; 94%) preferred granisetron ($P < 0.001$). Around 80% of the granisetron-treated patients in both groups required only a single prophylactic dose of granisetron. Following the first additional dose of granisetron, around 87% of patients reported symptoms to be improved or resolved. Adverse experience reporting was higher in the comparator groups with somnolence and extrapyramidal reactions representing the most common events. Headache was the most commonly reported adverse experience in granisetron-treated patients. Granisetron has proved safe and effective in controlling chemotherapy-induced emesis and is more convenient to administer than conventional antiemetics.
Eur J Cancer, Vol. 28A, Suppl.1, pp. S12-S16, 1992.

INTRODUCTION

CONTROL of nausea and vomiting is an important issue to cancer patients receiving cytotoxic chemotherapy [3]. Poor emetic control in the initial cycle of chemotherapy predisposes to poor response to antiemetics in subsequent cycles [4] and may cause patients to refuse further potentially life-saving treatment [5].

Experience with conventional antiemetic agents has led to them being administered in appropriate combinations in order to obtain superior efficacy to that observed with single agents [6]. Combinations have usually involved a steroid component, most commonly dexamethasone. One of the most effective of these combinations is high-dose metoclopramide plus dexamethasone which has proved effective antiemetic cover in patients receiving highly emetogenic cisplatin chemotherapy [6]. However, when used in doses high enough for adequate antiemetic effect, metoclopramide is also associated with distressing extrapyramidal side effects [7]. It was recognised that at these high doses, activity was mediated not by dopamine antagonism but via 5-HT_3 antagonism and this led to the development of 5-HT_3 antagonists as a new class of antiemetic agents [8].

Correspondence to: M. Marty
M. Marty is at Service d'Oncologie Médicale, Hôpital Saint Louis, 75010, Paris, France.

Granisetron is a highly selective and potent 5-HT_3 antagonist developed specifically for the management of emesis. Granisetron has been shown to be effective both in prevention of symptoms and in re-establishing emetic control. In a placebo-controlled study in patients receiving cisplatin chemotherapy a single dose of granisetron prevented vomiting in 93% (13/14) of patients [9]. In the placebo group rescue doses of granisetron gave resolution or improvement of symptoms within a few minutes of infusion [9].

Phenothiazines are the oldest group of drugs with proven antiemetic efficacy and chlorpromazine is one of the best known drugs in this group [5]. A single study has shown chlorpromazine in combination with dexamethasone to be comparable to high-dose metoclopramide plus dexamethasone [10]. However, chlorpromazine was associated with a high incidence of drowsiness and in this crossover study 65% of patients preferred metoclopramide plus dexamethasone.

In the following parallel-group studies granisetron has been compared with combinations of conventional antiemetics in the acute control of emesis in patients receiving both cisplatin and moderately emetogenic chemotherapy. Preliminary data from both studies was presented at ECCO5 in 1989 [1, 2]. This paper reports the results on the total number of patients enrolled into the two studies. In addition, data are presented on a subset of patients from one study who were crossed over to receive the alternative antiemetic regimen in their next cycle of

Table 1. Granisetron vs. chlorpromazine plus dexamethasone - minimum cytotoxic regimen

● Carboplatin	≥ 300 mg/m²
● Cisplatin	≥ 20 mg/m² to < 50 mg/m²
● Cyclophosphamide	≥ 600 mg/m²
● Dacarbazine	≥ 350 mg/m² to < 500 mg/m²
● Doxorubicin	≥ 40 mg/m²
● Epirubicin	≥ 75 mg/m²
● Mustine	≥ 6 mg/m²

chemotherapy in order to assess patient preference.

Efficacy was assessed primarily in terms of complete response which is defined as no vomiting and no worse than mild nausea. Nausea is a distressing symptom for the cancer patient [3] and moderate or severe nausea in the absence of vomiting cannot be considered as complete response.

PATIENTS AND METHODS

Granisetron was compared with metoclopramide plus dexamethasone in patients receiving highly emetogenic cisplatin chemotherapy and with chlorpromazine plus dexamethasone in patients receiving moderately emetogenic chemotherapy.

Patient selection

All patients were aged at least 16 years, had confirmed malignant disease, were naive to chemotherapy and gave their informed consent to participate in the study. Patients were excluded from the study if they had marked hepatic dysfunction, renal dysfunction, active peptic ulcer, gastric compression or already suffered from acute or chronic nausea and/or vomiting. Patients taking medication with effects on the central nervous system were not eligible for the study if they had any change in dosing regimen over the week before the study. Patients were screened for eligibility and randomly assigned to receive either granisetron or the comparator antiemetic in a single-blind fashion.

Cytotoxic chemotherapy regimens

In the cisplatin study patients were included if they were due to receive > 49 mg/m² cisplatin. In the other study the minimum cytotoxic regimen was defined in order to achieve a similar emetogenic potential in all patients (Table 1). Additional cytotoxics were permitted in line with their usual dosing schedule.

Antiemetic treatment

In both studies granisetron was given at a prophylactic dose of 40 μg/kg as a 5-min infusion to complete 5 min before the start of cytotoxic chemotherapy. Up to two further doses of granisetron were permitted within 24 h of starting chemotherapy if required for breakthrough symptoms of nausea and vomiting. The reason for administering any additional doses of granisetron and the outcome was recorded.

In the comparator groups dexamethasone was given prophylactically at a dose of 12 mg. In addition, patients received either metoclopramide, 3 mg/kg (i.v.) before chemotherapy followed by 4 mg/kg over 8 h, or chlorpromazine, 25 mg before chemotherapy (i.m. or i.v.) followed by oral chlorpromazine at 4-6 h intervals to a maximum dose of 200 mg within the 24-h study period. Antiemetic medication was not provided after the initial 24-h study period.

Efficacy evaluation

The patient's own subjective assessment of nausea and vomiting was recorded over the preceding 6-h period, at the commencement of chemotherapy and at 6, 12, 18 and 24 h after the start of chemotherapy. The time of first breakthrough of any nausea and vomiting was recorded. After 24 h patients were given a diary card on which to record their symptoms of nausea and vomiting on a daily basis over the next 6 days.

Crossover analysis

In the study comparing granisetron with chlorpromazine plus dexamethasone, 40 patients randomised to treatment at one centre were crossed over on their next cycle of chemotherapy to receive the alternative antiemetic regimen. At the 7-day follow up of the second cycle of chemotherapy patients were asked which antiemetic regimen they preferred.

Safety assessments

Blood pressure, pulse rate and temperature were recorded at screening, just before starting chemotherapy and at 6-h intervals over the 24-h study period. Blood and urine samples were taken at screening, before chemotherapy and at the end of the 24-h study period. Follow-up assessments were also carried out 7 days after chemotherapy. Patients were monitored for adverse events throughout this period.

Statistical analysis

All patients were included in the analysis of safety and efficacy. Patients' antiemetic responses in the 24-h period after the start of chemotherapy were classified according to the following criteria -

Complete responder:	Patients who experienced no vomiting and no or only mild nausea
Major responder:	Patients with just one episode of vomiting or no vomiting but with moderate or severe nausea
Minor responder:	Patients who vomited 2-4 times, regardless of their nausea rating
Failures:	Patients who vomited more than 4 times

Statistical analyses was performed using the chi-square test and Cox Log Rank test with a two-sided significance level of 5%.

RESULTS

Demographics

In both studies there were no significant differences between the treatment groups which were well balanced with regards to gender and age of patients (Table 2). In the cisplatin study the mean dose of cisplatin was comparable for both treatment groups.

Cisplatin chemotherapy

Cisplatin infusion times ranged from 15 min to 8 h with a mean time of 2.7 h. 5 patients in each group did not receive the minimum dose of cisplatin specified in the protocol (49 mg/m²).

Table 2. Patient demographics

	Cisplatin-based chemotherapy		Moderately emetogenic chemotherapy	
	Granisetron	Met/Dex	Granisetron	Chlor/Dex
No. of patients	143	138	133	133
Male	99	84	46	44
Female	44	54	87	89
Mean age (years) (Range)	56.6 (17-82)	54.8 (17-82)	55.0 (18-81)	53.8 (20-77)
Mean cisplatin dose (mg/m²)	86	84	-	-

In the 24 h after the start of cisplatin 100/143 (70%) of patients treated with granisetron were complete responders compared with 93/138 (67%) of patients receiving metoclopramide plus dexamethasone. The percentages of patients who were vomit free in this period were 76% for granisetron and 68% for the comparator. More of the granisetron-treated patients were major responders (85%) than the comparator group (77%) and there were fewer treatment failures following treatment with granisetron (4% vs. 11%). Efficacy at different dose levels of cisplatin is presented in Fig. 1. Complete and major efficacy was maintained across all doses of cisplatin and in patients receiving more than 100 mg/m² of cisplatin treatment, failure was higher in the comparator group than in granisetron-treated patients; 13% vs. 3%.

Additional doses of granisetron. 30 patients in the granisetron group received additional doses of granisetron but in 3 of these patients the first additional dose was given for mild nausea only. 2 patients were given additional doses of granisetron more than 24 h after the start of cisplatin. In 15 patients symptoms were resolved and in 11 patients symptoms were improved. 8 patients went on to receive a second additional dose of granisetron and in 5 of these symptoms were improved or resolved.

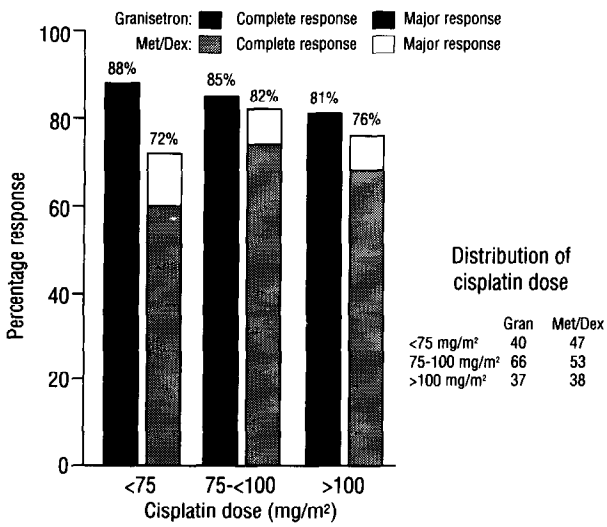

Fig. 1. Granisetron vs. metoclopramide plus dexamethasone - 24-h efficacy by dose of cisplatin.

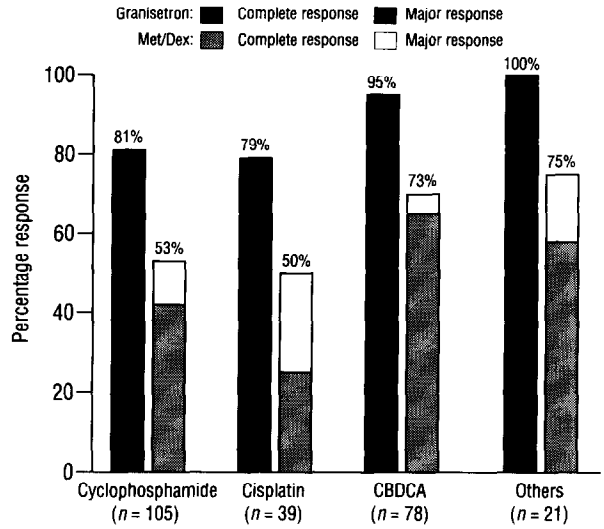

Fig. 2. Granisetron vs. chlorpromazine plus dexamethasone - 24-h major efficacy response by major cytotoxic regimens.

7-day efficacy. There was no significant difference between the two treatment groups with regard to complete response over 7 days. Thirty-six per cent of the granisetron group and 47% of the comparator group were still complete responders at the end of the 7-day period. Rescue antiemetics i.e. non-protocolled medication was required by 28% of granisetron-treated patients and 20% of the comparator group over the entire 7-day study period.

Moderately emetogenic chemotherapy

Patients received a wide range of chemotherapy in combination with the cytotoxics specified in the protocol. 3 granisetron-treated patients and 5 comparator-group patients did not receive cytotoxics as detailed in the protocol. In the 24 h after the start of chemotherapy 90/133 (68%) of granisetron-treated patients and 63/133 (47%) of patients receiving chlorpromazine plus dexamethasone were complete responders. Seventy-two per cent of the granisetron group and 53% of the comparator group were vomit-free at 24 h. Complete and major responses were seen in 86% of the granisetron group and 60% of patients treated with chlorpromazine plus dexamethasone. There were significantly fewer treatment failures in the granisetron group, 5%, compared to the comparator group, 21% ($P < 0.001$). Fig. 2 shows the efficacy response for the major classes of chemotherapy the patients received in this protocol. The response was consistent across all of these chemotherapy regimens.

Additional doses of granisetron. 25 patients in the granisetron group required additional doses of granisetron. 13 of these patients reported an outcome of resolved and 9 reported improved symptoms following a single dose of granisetron. 9 patients received a second additional dose and in 7 of these the outcome was improved or resolved.

7-day efficacy. At the 7-day follow-up visit 50% of granisetron-treated patients and 36% of the comparator group were still complete responders. There was a significant difference in the survival distributions of time to less than

Table 3. Granisetron vs. chlorpromazine plus dexamethasone - crossover analysis and patient preference

	Granisetron	Chlor/Dex	P
No. of patients with a complete response at 24 h in both cycles	22 (56.4%)	10 (25.6%)	0.022
Patient preference[a]	32/34 (94.1%)	2/34 (5.9%)	< 0.001

No. of patients completing both treatments = 39.
[a]The number of patients preferring a particular therapy expressed as a ratio of the total no. of patients giving preference.

complete response; $P = 0.0027$. Eighteen per cent of granisetron-treated patients and 14% of the comparator group took antiemetics above that specified in the protocol over the 7-day period.

Crossover analysis. Of the 40 patients participating in the crossover section of this study, 39 completed both cycles of chemotherapy. The 24-h efficacy response in this subset of patients was significantly higher following treatment with granisetron (56%) than chlorpromazine plus dexamethasone (26%; Table 3; $P = 0.022$). 34 of these patients expressed a preference for one of the antiemetic regimens. A significant majority preferred granisetron to the comparator antiemetics (32/34; $P < 0.001$; 82% of all patients).

Safety

The adverse-experience profile in granisetron-treated patients from both studies was very similar. Table 4 shows the most commonly reported adverse events for the comparator groups and pooled data for the granisetron patients. All other adverse experiences occurred in < 5% of patients.

Adverse-event reporting was significantly higher in the chlorpromazine plus dexamethasone group than in the granisetron patients. Headache was the most commonly reported adverse event in patients receiving granisetron (12%) and no patients reported extrapyramidal-like reactions. Somnolence was significantly higher in both comparator groups compared with granisetron.

Adverse-experiences led to withdrawal from clinical assessments prior to completion of the 24-h study period in 2 granisetron-treated patients i.e. for headache which was considered by the investigator to be probably related and cardiac arrest which was considered unlikely to be related to granisetron therapy. 2 patients receiving metoclopramide plus dexamethasone were withdrawn from the study due to adverse events which were dyspnoea, tachycardia and pericarditis in 1 patient and extrapyramidal reactions in the other. 13 patients in the chlorpromazine plus dexamethasone group were withdrawn due to adverse events, 12 experiencing somnolence and 1 patient experienced syncope.

2 granisetron-treated patients died within the 7-day assessment period and a further 3 patients died on days 8 and 9. None of the deaths were considered to be related to granisetron. 1 patient receiving metoclopramide plus dexamethasone died on day 6 but again this was assessed as unrelated to the study antiemetic therapy.

Table 4. Adverse-event profile

	Granisetron ($n = 276$)	Met/Dex ($n = 138$)	Chlor/Dex ($n = 133$)
Patients with adverse events	63 (23%)	45 (33%)	47 (35%)*
Headaches	32 (12%)	4 (3%)*	8 (6%)*
Diarrhoea	4 (1%)	10 (7%)*	4 (3%)
Somnolence	2 (1%)	7 (5%)*	22 (17%)*
CNS stimulation/ extrapyramidal effects	0	18 (13%)*	0

*$P < 0.04$ compared with the granisetron group.
Abbreviations: CNS, central nervous system.

Analysis of laboratory data demonstrated no clinically significant differences between the granisetron and comparator groups. Mean changes in vital signs were small and similar between treatment groups and there were no significant differences.

DISCUSSION

In these two comparative studies a single prophylactic dose of granisetron, a highly selective 5-HT_3 antagonist, has proved to be at least as effective as two combination regimens of conventional antiemetics with around 70% of patients experiencing no vomiting and no worse than mild nausea within 24 h of starting cytotoxic chemotherapy. Around 80% of granisetron patients required only a single prophylactic dose making this regimen far more convenient than the multidose comparator regimens. Additional doses of granisetron given for breakthrough symptoms of nausea and vomiting were effective in re-establishing control. Around 88% of patients reported symptoms to be improved or resolved following the first additional dose and at least 63% following a second additional dose which was only required by 7% of granisetron-treated patients. Efficacy was maintained at high cisplatin doses and across various moderately emetogenic chemotherapy regimens (Figs. 1 and 2). When patients receiving moderately emetogenic chemotherapy were crossed to receive both granisetron and chlorpromazine plus dexamethasone 94% of patients who expressed a preference preferred granisetron (Table 3). In this crossover analysis the complete responder rates were lower than in the main protocol. The lower response rate in this crossover group was probably due to the higher proportion of female patients (12:1) compared to the study as a whole (2:1). It is well established that gender is an important factor in antiemetic response with females proving more difficult to control than males [11].

In those patients where breakthrough of vomiting occurred, twice as many patients in the comparator groups had vomited within 12 h of the start of chemotherapy compared to the granisetron-treated patients. In the cisplatin study, 27% and 13% of comparator and granisetron patients vomited respectively within 12 h while in patients receiving moderately emetogenic chemotherapy 39% and 20% in the comparator and granisetron groups had vomited within 12 h.

Over the entire 7-day assessment period in patients receiving moderately emetogenic chemotherapy more granisetron-treated

patients maintained complete-response compared to the comparator group (50% vs. 36%; $P = 0.0027$). However, in cisplatin patients the 7-day complete-responders rate was higher for the metoclopramide plus dexamethasone-treated patients (47% vs. 36%) but this difference was not statistically significant. This difference may be due to a prolonged action of the prophylactic dose of dexamethasone which has been shown to be effective in controlling delayed nausea [12].

Adverse-experience reporting was significantly lower in granisetron-treated patients compared to those receiving chlorpromazine plus dexamethasone. Granisetron was not associated with extrapyramidal reactions which were reported by 13% of patients receiving metoclopramide plus dexamethasone. Constipation has been reported in volunteers treated with granisetron and cytotoxic chemotherapy is known to cause diarrhoea. The lower incidence of diarrhoea reported in the granisetron patients is probably explained by this constipatory action of granisetron.

In conclusion, granisetron, a highly selective 5-HT_3 antagonist, proved both safe and effective in the prophylaxis and control of emesis induced by a variety of chemotherapeutic regimens. A simple, single 5-min infusion of granisetron was more convenient to administer than the multi-dose comparator regimens. Furthermore, granisetron is preferred by a significant majority of patients and represents a major advantage in the clinic.

1. Marty M on behalf of the Granisetron Study Group. A comparative study of the use of granisetron, a selective 5HT-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-S33.
2. 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-S37.
3. 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.
4. Roila F, Tonato M, *et al.* Protection from nausea and vomiting in cisplatin-treated patients: High-dose metoclopramide combined with methylprednisolone versus metoclopramide combined with dexamethasone and diphenhydramine: A study of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1989, 7, 1693-1700.
5. O'Brien MER, Cullen MH. Are we making progress in the management of cytotoxic drug-induced nausea and vomiting? *J Clin Pharmacol Ther* 1988, **13**, 19-31.
6. Gralla RJ, Tyson LB, Kris MG, et al. The management of chemotherapy-induced nausea and vomiting. *Med Clin N Am* 1987, **71**, 289-301.
7. Miller LG, Jankovic J. Metoclopramide-induced movement disorders: Clinical findings with review of the literature. *Arch Intern Med* 1989, **149**, 2486-2492.
8. Miner WD, Sanger GJ, Turner DH. Evidence that 5-hydroxytryptamine$_3$ receptors mediate cytotoxic drug and radiation-evoked emesis. *Br J Cancer* 1987, **56**, 159-162.
9. Cupissol DR, Serrou B, Caubel M. The efficacy of granisetron as a prophylactic antiemetic and intervention agent in high-dose cisplatin-induced emesis. *Eur J Cancer* 1990, **26**, (Suppl.1), S23-S27.
10. Gez E, Ben-Yosef R, Catane R, *et al.* Chlorpromazine and dexamethasone versus high-dose metoclopramide and dexamethasone in patients receiving cancer chemotherapy, particularly cisplatinum: A prospective, randomised, crossover study. *Oncology* 1989, **46**, 150-154.
11. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials. A review. *Annals Oncol* 1991, **2**, 107-114.
12. Roila F, Boschetti E, Tonato M, *et al.* Predictive factors of delayed emesis in cisplatin-treated and antiemetic activity and tolerability of metoclopramide or dexamethasone. *Am J Clin Oncol* 1991, **14**, 238-242.