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Eur J Cancer, Vol. 28A, Suppl. 1, pp. S28-S32, 1992
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

Oral Granisetron - Simple and Effective: A Preliminary Report

Anne Hacking
on behalf of the Granisetron Study Group

This randomised, double-blind, study was carried out in 930 patients in order to examine the efficacy and safety of oral granisetron in the dose range 0.25, 0.5, 1.0 and 2.0 mg twice daily. Oral granisetron was administered for either 7 or 14 days according to the chemotherapy regimen used. A total of 930 patients were enrolled into this study in order to be able to detect a difference of 15% between groups (80% power). The preliminary results showed that at 7 days efficacy was significantly greater for 1.0 mg b.d. (58.5%) than for 0.25 mg b.d. (43.7%) and indicated that, of the doses examined, the 1.0 mg b.d. dose was optimal in patients receiving moderately emetogenic chemotherapy. In agreement with this there were more withdrawals from the 0.25 and 0.5 mg groups due to lack of efficacy. The adverse events most frequently reported (in > 5% of patients) were constipation, headache, abdominal pain, fever, leucopenia and asthenia. The latter three are recognised side effects of the primary disease and of chemotherapy. The incidence of headache was similar to that seen in previous granisetron studies. Abdominal pain may have been related to constipation. The incidence of constipation (25.9%) was higher than that reported in previous granisetron studies but was not dose related. Thus oral granisetron at 1.0 mg twice daily is an effective antiemetic, offering a convenient dosing regimen without significant adverse events.
Eur J Cancer, Vol. 28A, Suppl. 1, pp. S28-S32, 1992.

INTRODUCTION

PATIENTS receiving chemotherapy for malignant disease have noted the most severe side effects of this treatment as being vomiting and nausea [1]. These side effects have a number of important implications, both for the patients' quality of life and because of further medical complications such as dehydration, electrolyte imbalance, malnutrition, vitamin deficiencies and oesophageal tears [2]. However, the most important consequence of severe nausea and vomiting is that patients may refuse further potentially curative chemotherapy [2], in which case these side effects assume a potentially lethal toxicity [3].

A variety of antiemetic drugs have been used to treat chemotherapy-induced emesis, these include dopamine-receptor antagonists, synthetic cannabinoid derivatives and other drugs which facilitate their antiemetic action (e.g. dexamethasone, lorazepam) [4]. While dopamine-receptor antagonists are effective against the mild-to-moderate emesis evoked by some cytotoxics, they offer little protection against the more severe emesis evoked by drugs such as high-dose cisplatin [4]. Metoclopramide is an exception to this, as it is effective, at high doses, against cisplatin-induced emesis. This action is mediated by antagonism of 5-HT_3 receptors rather than dopamine-receptor antagonism [5]. The problem of using high doses of metoclopramide are the serious extrapyramidal side effects associated with its use [2, 6, 7].

Recognition that high-dose metoclopramide mediated its antiemetic effects via 5-HT_3 receptor antagonism led to the identification of the serotonin-3 receptor antagonists as a new class of antiemetic agents [8]. Granisetron is a specific [9] and extremely potent [8] 5-HT_3 receptor antagonist which has been developed as an intravenous (i.v.) drug and is currently under development as an oral formulation.

Three pilot studies have already been performed in order to determine the antiemetic efficacy of various oral doses of

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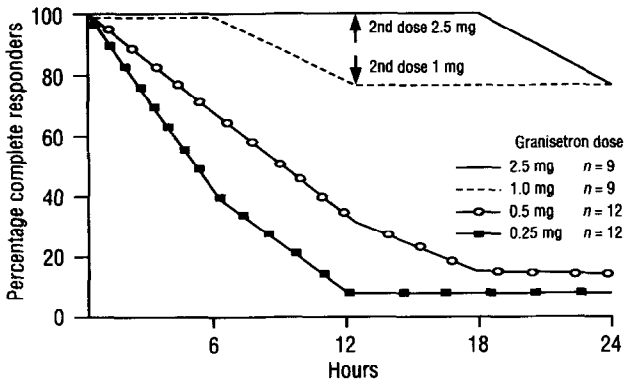


Fig. 1. Percentage of complete responders after treatment with granisetron over 24 h in pilot studies.

granisetron. These studies were all carried out in patients receiving cisplatin chemotherapy (≥ 50 mg/m²), two were fixed-dose studies with granisetron doses of 0.25 mg or 0.5 mg once daily. The other study examined granisetron doses of 2.5 mg or 1.0 mg administered twice daily. The results of these studies are depicted graphically in Fig. 1. While twice-daily dosing with 2.5 mg of granisetron offered complete control of emesis in all patients for up to 18 h following chemotherapy, a dose of 0.25 mg appeared to be sub-optimal. Doses above 2.5 mg did not offer any significant improvement in the percentage of complete responders (data on file), thus suggesting that the optimal oral dose of granisetron lay somewhere between 2.5 and 0.25 mg twice daily. Based on this information, a large multinational oral dose-ranging study was set up to define the optimal oral dose of granisetron in patients receiving moderately emetogenic chemotherapy. From the results of the pilot studies (Fig. 1) there was a clear fall-off in efficacy at 12 h with the lower doses studied, thus a twice-daily dosing was chosen. The doses of granisetron chosen for the study were 0.25, 0.5, 1.0 and 2.0 mg twice-daily, the aim was to recruit 800 evaluable patients to investigate the 7-day response rate. In this paper the preliminary efficacy and safety data are presented.

Table 1. Patients receiving one of the following cytotoxic treatment regimens were eligible for inclusion into the study. Other (less-emetogenic) cytotoxics could also be given in combination with one of these primary regimens

Oral		
Cyclophosphamide	≥ 100 mg/m²	Days 0-13 inclusive (when in combination with other cytotoxic drugs on days 0 & 7)
Intravenous		
Cyclophosphamide	≥ 500 mg/m²	Day 0 or days 0 & 7 (when in combination with other cytotoxic drugs)
Carboplatin	≥ 300 mg/m²	Day 0 or days 0 & 7
Cisplatin	≥ 20 mg/m² ≤ 50 mg/m²	Day 0 or days 0 & 7
Dacarbazine	≥ 350 mg/m² < 500 mg/m²	Day 0 or days 0 & 7
Doxorubicin	≥ 40 mg/m² single agent ≥ 25 mg/m² in combination with other cytotoxics	Day 0 or days 0 & 7
Epirubicin	≥ 75 mg/m² single agent ≥ 50 mg/m² in combination with other cytotoxics	Day 0 or days 0 & 7

PATIENTS AND METHODS

This multicentre, multinational, double-blind, randomised study was intended to recruit 800 chemotherapy-naive patients. The patients recruited were to be over the legal age of consent, to have given informed consent to participate and to have had a WHO performance status scale grade of 2 or less. The allowed chemotherapy regimens for inclusion into the study are given in Table 1.

Reasons for exclusion from the study included hepatic dysfunction, renal dysfunction, cardiac failure, a primary or secondary brain tumour, active peptic ulcer or gastric compression, cardiac failure and pre-existing acute or chronic nausea and vomiting. Other reasons for exclusion were changes in the medication/dosage of central nervous system (CNS) active drugs and scheduled treatment with corticosteroids, radiotherapy, other antiemetics or any new chemical entity during the study period.

Chemotherapy

Patients who were scheduled to receive one of the primary chemotherapy regimens listed in Table 1 as treatment for malignant disease were eligible for inclusion into the study. Patients were scheduled to receive i.v. chemotherapy on day 0 only, i.v. chemotherapy on days 0 and 7 or oral cyclophosphamide for 14 days. In addition to the primary chemotherapy regimens listed, other less emetogenic chemotherapy could be given in combination on day 0 or on days 0 and 7.

Study drug administration

Patients were randomised in a double-blind fashion to receive 0.25, 0.5, 1.0 or 2.0 mg of granisetron twice daily. The first granisetron capsule was taken 1 h prior to the start of chemotherapy, subsequent capsules were taken at 12-h intervals. For those patients who received i.v. chemotherapy on day 0 only, oral granisetron was given for 7 days. For patients who received i.v. chemotherapy on days 0 and 7 or 14 days treatment with oral cyclophosphamide, oral granisetron was given for 14 days. Thus, granisetron treatment divided patients into two discrete populations.

Rescue medication

In cases where adequate control of emesis was not obtained with the study medication, such that further treatment was thought necessary, the patient was withdrawn from the study and other standard antiemetics of the physicians' own choice were administered.

Data collection

Patients could be discharged from hospital 1 h after the start of cytotoxic therapy. Patients were provided with diary cards on which daily assessments of nausea and vomiting were recorded. Nausea was noted as none, mild, moderate or severe on each day while the number of vomiting episodes were recorded as none, 1, 2, 3, 4 or > 4 times. Retching was considered equivalent to vomiting when making these assessments.

Diary cards were used for either 1 or 2 weeks to record information during the study treatment period.

Table 2. Efficacy criteria

Complete responder:	No vomiting and no worse than mild nausea, no rescue medication and not withdrawn during the study period.
Major responder:	1 vomit and/or moderate to severe nausea
Minor responder:	2 - 4 vomits
Failure:	> 4 vomits

Vomit = retch.

Data analysis

In this preliminary analysis the primary efficacy assessment was the percentage of complete responders over the first 7 days as this period includes all patients.

A total of 200 patients per group were estimated to be sufficient to detect a difference of 15% between groups (assuming 5% significance level with Bonferroni correction for multiple comparisons: at least 80% power). Prospectively, "treated patients" were defined as those who had received any study medication while "evaluable patients" were those treated patients for whom any assessable data were available. It was also decided prospectively that when no assessable data were available due to either patient withdrawal or missing assessments, then the patient would be assumed to have failed.

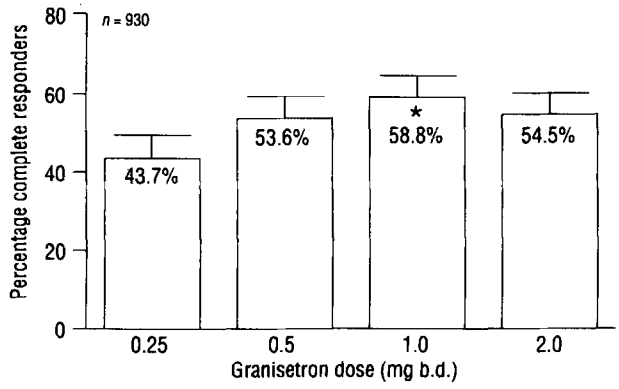
The statistical tests used to analyse the data included the chi-square test and the Cox Log Rank test. In both of these tests, a two-tailed significance level of 5% was regarded as statistically significant. For the 7-day efficacy results the Bonferroni correction was employed in order to maintain the overall two-tailed significance level of 5% (i.e. for each pairwise comparison a two-tailed significance level of 0.83% was used to determine whether the result was to be regarded as statistically significant.

Efficacy criteria

Complete responders were defined as patients who experienced all of the four following criteria:

- no vomiting
- no worse than mild nausea
- received no rescue medication
- were not withdrawn during the treatment period (either 7 or 14 days).

Major responders were patients who experienced one vomiting episode and/or moderate to severe nausea. Minor responders were those who experienced 2-4 vomiting episodes regardless of nausea rating. Failures were those who experienced > 4 vomiting episodes. Retching was considered equivalent to vomiting for the purpose of this evaluation (Table 2).



*Denotes statistically different ($P < 0.05$) to the 0.25 mg group.

Fig. 2. Percentage of complete responders in each granisetron dosage group over the first 7-day treatment period.

Table 3. Patient demographics by granisetron dosage group

	Granisetron dose (mg twice daily)				
	0.25	0.5	1.0	2.0	All
Total patients recruited	229	235	233	233	930
Male	31	28	28	30	117
Female	198	207	205	203	813
Mean age (years)	52	51	53	51	52
Mean weight (kg)	66	66	65	66	66
Primary cytotoxic -					
oral cyclophosphamide	34	38	35	38	145
other i.v. chemotherapy	195	197	198	195	785

RESULTS

A total of 930 patients received study medication. Key demographic data are shown in Table 3, by granisetron dosage group. Many more females than males were recruited. However, the distribution of males and females was approximately equal across the four groups.

Efficacy

The percentage of complete responders in each study group over the first 7-day study period is shown graphically in Fig. 2. There were significantly more complete responders in the 1.0 mg twice daily group (59%) than in the 0.25 mg twice daily group (44%). The percentage of complete responders was not, however, significantly different between either the 0.25 and 0.5 mg twice daily group or between the 1.0 and 2.0 mg twice daily groups ($P < 0.05$) as the confidence intervals for these comparisons do not include zero. From Table 4, it can be seen that there was a trend approaching statistical significance at between the 0.25 mg twice daily and 2.0 mg twice daily groups.

During the first 7-day treatment period a total of 82 patients were withdrawn from the study. Details of the reasons for withdrawal are shown in Table 5. The number of patients withdrawn due to lack of efficacy was higher in the 0.25 mg, 0.5 mg and 2.0 mg groups than in the 1.0 mg group. There was no significant difference in the overall number of patients withdrawn from each of the study groups.

The percentage of patients who reported adverse events during the entire study period (i.e. up to the final follow-up visit) was similar across all dosage groups. The most frequent adverse events (those occurring in > 5% of patients) are listed in Table 6. These were headache, constipation, fever, leucopenia,

Table 4. Simultaneous 95% confidence intervals (Bonferroni) of pairwise difference between treatment groups in 7-day complete response rates

Comparison	Lower	Upper
0.25 mg vs. 0.5 mg	-0.2101	0.0111
0.25 mg vs. 1.0 mg	-0.2614	-0.0412
0.25 mg vs. 2.0 mg	-0.2191	0.0024
0.5 mg vs. 1.0 mg	-0.1615	0.0579
0.5 mg vs. 2.0 mg	-0.1192	0.1014
1.0 mg vs. 2.0 mg	-0.0669	0.1528

Table 5. Withdrawals from the study during the first 7-day treatment period

	Granisetron dose (mg twice daily)			
	0.25	0.5	1.0	2.0
No. per group	229	235	233	233
No. withdrawn	27	22	11	22
Reason for withdrawal:				
Lack of efficay	21	10	3	6
Lack of efficacy and adverse events	4	2	2	2
Significant adverse events	0	2	1	2
Lack of compliance	1	2	1	5
Protocol violation	1	3	4	2
Other	0	3	0	5

NOTE: Other = concurrent disease/patient deterioration/significant adverse events + protocol violation/other reasons

abdominal pain and asthenia. There was no significant difference in the incidence of any of these adverse events across the four dosage groups ($P < 0.05$). Overall these results underwrite 1.0 mg twice daily as the optimal clinical dose.

DISCUSSION

The efficacy results over the first 7-day period indicate that, of the four oral dose studies, the 1.0 mg twice-daily dose was the most effective granisetron treatment regimen. The 7-day complete response rate in the 0.25 mg group (43.7%) was, as expected, the lowest. The 7-day complete response rate in the 0.5 mg group (53.6%) was not significantly different to that of the 0.25 mg group while that of the 1.0 mg group (58.8%) was significantly higher ($P < 0.05$) (Fig. 2).

The complete response rate in the 2.0 mg group was marginally lower than that of the 1.0 mg group, although not significantly so. As the 95% confidence intervals overlap, this slightly lower response rate in the 2.0 mg group probably represents the variations seen on the plateau of the dose-response curve. Thus, these results indicate that the best granisetron dose is 1.0 mg twice daily and there is no advantage in increasing the dose above this.

The optimal 7-day complete response rate, observed with the 1.0 mg group was 59% with these moderately emetogenic chemotherapy regimens. One factor which might be considered here is the patient demography (Table 3), 87% of the patient population in this study was female and it is known that gender is an important factor, since females are known to vomit more than males [10]. Despite this predominance of females in the patient population the study showed a good response rate to oral granisetron.

The table of withdrawals (Table 5) shows that more patients were withdrawn from the lower dosage groups (0.25 and 0.5 mg twice daily) due to lack of efficacy. This is consistent with the higher dose of 1.0 mg twice daily being optimal. The other reasons for withdrawal do not show any noteworthy pattern across the four dosage groups.

The adverse-experience profile for the study is shown in Table 6, of all patients 68.6% reported adverse events during the course of the study. There was no significant difference in the incidence of adverse events across the four dosage groups ($P < 0.05$). It should be noted that, while efficacy results for the first 7 days of treatment are presented, the adverse events table refers to those reported at any time up to the final follow up.

Table 6. Adverse-event profile

	Granisetron dose (mg twice daily)			
	0.25 ($n = 229$)	**0.5** ($n = 235$)	**1.0** ($n = 233$)	**2.0** ($n = 233$)
Total no. with adverse experiences (%)	152 (66.4)	164 (69.8)	161 (69.1)	161 (69.1)
Constipation	49 (21.4)	69 (29.4)	59 (25.3)	64 (27.5)
Headache	48 (21.0)	42 (17.9)	39 (16.7)	41 (17.6)
Leucopenia	24 (10.5)	30 (12.8)	33 (14.2)	35 (15.0)
Abdominal pain	12 (5.2)	24 (10.2)	19 (8.2)	21 (9.0)
Asthenia	20 (8.7)	25 (10.6)	20 (8.6)	16 (6.9)
Fever	22 (9.5)	12 (5.1)	14 (6.0)	11 (4.8)

The most frequently reported adverse events (occurring in > 5% of patients), as shown in Table 6, were constipation, headache, abdominal pain, leucopenia, asthenia and fever, the latter three probably being related to the patient's primary condition or to the chemotherapy.There was no significant difference in the incidence of any of these individual adverse events across any of the dosage groups, this was consistent with the conclusion for adverse events overall, that incidence was not increased with increasing granisetron dosage.

Leucopenia is a recognised side effect of chemotherapy [11], fever is also a common occurrence in cancer patients. Asthenia is another recognised side effect of chemotherapy, feeling low/miserable (depression) and being constantly tired were two of the symptoms frequently reported in the study of patient perception of side effects by Coates *et al.* [1].

The other most commonly reported adverse events in this study were headache, constipation and abdominal pain. The former two are both recognised side effects of granisetron administration. The overall incidence of headache (18.3%) was similar to that reported in previous i.v. studies, both for single-day [12] and multiple-day [13] granisetron administration. Overall this tends to suggest that repeated granisetron administration does not cause increased incidence of headache. Similarly the incidence of constipation and of abdominal pain did not differ significantly across the four dosage groups ($P = 0.238$ and $P = 0.246$, respectively). The overall incidence of constipation was 25.9% which was higher than that reported in previous studies. Previous studies with i.v. granisetron resulted in an incidence of constipation of ~3-4% in single-day studies [12] and an incidence of ~11-12% in studies where i.v. granisetron was given on 5 consecutive days [13]. The higher incidence of constipation seen after repeated oral administration of granisetron on consecutive days may suggest that repeated dosing leads to some sort of cumulative effect for this adverse event. However, without a comparator group it is difficult to assign causality to granisetron, chemotherapy or patient characteristics. The severity of constipation reported by the majority of patients was mild or moderate. Constipation was not defined during the course of the study and the incidence represents spontaneous reporting by the patients.

Extrapyramidal side effects, a common problem with dopamine antagonists, were not noted in any granisetron patients.

This dose-ranging study showed a 1.0 mg twice daily granisetron dosing regimen to offer optimum 7-day efficacy in

patients receiving moderately emetogenic chemotherapy. More patients were withdrawn from the lower-dosage groups (0.25 and 0.5 mg twice daily) due to lack of efficacy, also supporting the 1.0 mg twice daily dose. Of the most frequently reported adverse events, leucopenia, fever and asthenia were recognised side effects of the primary disease and chemotherapy. Headache occurred with similar incidence to that seen in previous granisetron studies.

While the incidence of constipation was higher in this study than in previous studies causality cannot be assessed due to the lack of a comparator. Thus, the results of this study indicate that oral granisetron, at 1.0 mg twice daily, is a safe and effective antiemetic in patients receiving moderately emetogenic chemotherapy. In addition, it offers a convenient dosing regimen.

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Eur J Cancer, Vol. 28A, Suppl. 1, pp. S32-S35, 1992
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

Are Granisetron and Ondansetron Equivalent in the Clinic?

Stephen Dilly

There are no published direct trials of granisetron vs. ondansetron. Difficulties exist in comparing reported trials because of differences in methodology, especially in response criteria. In this review, a comparison is made between ondansetron and granisetron by recalculating the complete response criterion for granisetron, standardising it against that in the ondansetron programme (i.e. no vomiting). Weighted means have been calculated for three areas of study. Against cisplatin-induced emesis the (weighted) mean percentage of complete responders were calculated at 64% (range 49-77%) for granisetron and 49% (range 40-55%) for ondansetron. Against moderately emetogenic stimuli, the response rates were 76% (range 68-80%) and 73% (range 60-87%) respectively. For fractionated chemotherapy the response rates were 57% and 27% for granisetron and ondansetron respectively. Although not shown by formal statistical analysis, these results suggest that a clinical advantage for granisetron may exist.
Eur J Cancer, Vol. 28A, Suppl.1, pp. S32-S35, 1992.

INTRODUCTION

THE ADVENT of the new 5-HT_3 receptor antagonists has greatly improved the quality of life of patients receiving emetogenic chemotherapy. However, the clinical availability of more than one such 5-HT_3 receptor antagonists leaves the clinician with a choice. To date, there have been no published studies which directly compare the efficacy and safety of granisetron and ondansetron. This presentation aims to compare the efficacy of these two compounds by a review of the published literature to provide an insight into what may be the best way clinically to compare these drugs. Tropisetron, for which relatively little data has been published, has, for this reason, not been considered in this review.

ASSESSMENT OF NAUSEA AND VOMITING

Comparison of the results of clinical trials between ondansetron and granisetron is fraught with difficulty because of differences in the criteria used to assess response rates

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