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A Single-Blind Study of the Efficacy and Safety of Intravenous Granisetron Compared with Alizapride Plus Dexamethasone in the Prophylaxis and Control of Emesis in Patients Receiving 5-day Cytostatic Therapy

Karl Bremer on behalf of the Granisetron Study Group*

200 cancer patients who were due to receive fractionated chemotherapy (cisplatin ≥ 15, ifosfamide ≥ 1.2 or etoposide ≥ 120, all mg/m² per day) for 5 days, entered a multicentre study. Patients were randomised single-blind to receive either prophylactic intravenous granisetron (40 μg/kg) or alizapride (4 mg/kg followed by 4 mg/kg at 4 and 8 h post-treatment) plus dexamethasone 8 mg. Granistron was superior to the combination in preventing nausea and vomiting (54% vs. 43% complete responders). The differences were in the cisplatin-treated group. The time to first episode of moderate to severe nausea was significantly longer in the granisetron group ($P = 0.03$). Dosing with granisetron was more simple, with over 85% of patients requiring only a single prophylactic dose. Fewer patients receiving granisetron experienced adverse events (48% vs. 62%, $P = 0.047$). The frequency of constipation was, as expected, significantly higher in the granisetron group. Extrapyramidal effects, which were not noted by any granisetron patient, occurred in 5.3% of comparator patients.
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INTRODUCTION

TREATMENT OF malignant diseases with cytostatic agents leads to a number of unwanted side-effects. Cytostatic drug-induced nausea and vomiting occur in the majority of patients. This presents an important clinical problem as not only does it reduce the patient's quality of life but it may cause the patient to refuse further cycles of chemotherapy [1]. There is thus a considerable need for effective antiemetic treatment for this group of patients.

Fractionated chemotherapy regimens have been developed for a variety of tumour types. The rationale behind these regimens is primarily focused on the reduction of toxic effects such as bone-marrow depression, neuropathy, nephropathy and emesis.

Combination treatments such as alizapride/dexamethasone are commonly used to prevent emesis [2]. Alizapride is a substituted benzamide, which in low doses blocks central dopamine D_2 receptors, but in high doses may be a 5-HT_3 antagonist [1]. Unfortunately, high dosage is also associated with extrapyramidal side-effects such as restlessness (frequently severe) [3]. Thus it is often used in conjunction with dexamethasone and benzodiazepines leading to enhanced anti-emetic efficacy and sedation [2].

Granisetron is a new antiemetic which is a potent and highly selective 5-HT_3 receptor antagonist free from dopamine D_2 receptor antagonist properties [4]. In the majority of patients receiving highly emetogenic cytostatic regimens, a single dose of granistron (40 μg/kg) has been shown to be effective in preventing or controlling nausea and vomiting during the subsequent 24 h [5]. The aim of this study was to compare the efficacy and safety of granisetron with the combination alizapride/dexamethasone in patients receiving cytostatic therapy for malignant disease on each day of a 5-day treatment period.

PATIENTS AND METHODS

Patients

This study was carried out at 25 centres in Belgium, France and Germany. Each patient was over the legal age of consent, had a Karnofsky index score of 60% or more [6], was naïve to chemotherapy and was due to receive moderately emetogenic cytostatic therapy for malignant disease (cisplatin ≥15 mg/m² or ifosfamide ≥1.2 g/m² or etoposide ≥120 mg/m²) on each day for 5 days. The patient had to receive the same main cytostatic agent on each day of treatment. Patients were excluded from the study if they had marked hepatic dysfunction, renal dysfunction,

cardiovascular disease, active peptic ulcer or gastric compression, a partial or generalised seizure within the last year, a primary or secondary brain tumour or pre-existing acute or chronic nausea and vomiting. Other reasons for exclusion were changes in medication/dosage of central nervous system (CNS)-active drugs and schedule treatment with corticosteroids, other antiemetics, radiotherapy or any new chemical entity during the study. All patients gave their informed consent to participate in the study and were free to withdraw at any time.

Protocol design

Patients were randomised in a single-blind fashion to receive either intravenous granisetron or alizapride/dexamethasone. The patients were allocated to one of the two antiemetic treatment schedules by reference to a predetermined randomisation list which was held centrally in order to avoid bias. The randomisation was stratified according to cytotoxic agent.

Cytostatic chemotherapy

Patients recruited into the study were due to receive fractionated chemotherapy over 5 days. 142 patients received cisplatin $\geq$15 mg/m^2/d [mean (S.D.) 20.00 (0.63)], 54 received ifosfamide $\geq$1.2 g/m^2/d [1.592 (0.030)] and one received etoposide $\geq$120 mg/m^2/day (128.36 same dose on each of 5 days). All patients were naïve to chemotherapy and each patient received the same main cytostatic agent on each day of treatment.

Granisetron

Patients allocated to granisetron received a dose of 40 μg/kg body weight as a 5 min intravenous infusion, to be completed 5 min before cytostatic therapy. In patients who experienced any vomiting or worse than mild nausea, up to two additional granistron doses (40 μg/kg infusion over 5 min) were allowed in 24 h.

Comparator

Patients receiving comparator medication received dexamethasone as a single 8 mg fixed dose 5 min prior to chemotherapy. Alizapride (4 mg/kg) was given as a 15 min intravenous infusion to complete 5 min before cytostatic therapy. Two further doses of alizapride (4 mg/kg) were given at 4 and 8 h after chemotherapy, thus the normal daily dosage was 12 mg/kg. In patients who experienced vomiting or worse than mild nausea, up to two additional doses of alizapride (4 mg/kg) were allowed

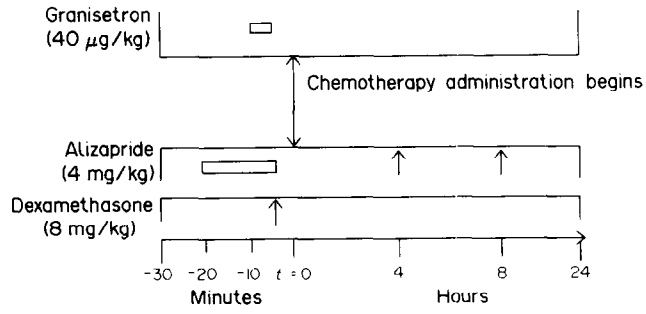

Fig. 1. Administration of antiemetic therapy.

(Fig. 1). For patients who responded well to the comparator medication (i.e. did not require rescue medication), but who experienced side-effects such as "restless syndrome", the dose could be decreased by 1 mg/kg every 24 h to a minimum of 1 mg/kg if necessary.

Patient withdrawal

In cases where adequate control of emesis was not obtained (in either group), the patient was withdrawn from the study and treated with other medication of the physician's own choice.

Assessment of efficacy

During the 5 days of chemotherapy the patient was kept in hospital and assessments of nausea, vomiting, appetite, state of alertness, general well being and vital signs were made prior to chemotherapy and then on a 6-h basis. A daily assessment of nausea and vomiting was made for a further 7 days by the use of diary cards. Nausea was rated as none, mild, moderate or severe. The number of vomiting episodes was recorded as none, 1, 2–4, or more than 4.

STATISTICAL ANALYSIS

The target sample size was 200, as 100 evaluable patients per group were sufficient to detect a difference of 19% between groups (5% significance level: at least 80% power) [7]. Prior to any analysis being performed, a set of criteria was drawn up to define "treated patients", "evaluable patients", the conditions under which patients would be included into the various analyses, and how withdrawals or missing assessments would be evaluated. These criteria are presented below.

Criteria for inclusion in analysis

"Treated patients" were defined as those who received any anti-emetic treatment, while "evaluable patients" are those treated patients for whom assessable data are available. Patients were included in the day-by-day analysis if they completed that day, in the 5-day analysis if they completed the 5 days, while in the survival analysis they were included up to the point where no further information was available.

Withdrawals

Any patients withdrawn due to lack of efficacy or an adverse event related to antiemetic therapy were included as failures at the appropriate point. Patients withdrawn due to deterioration of condition, change of chemotherapy regimen or an adverse event not related to antiemetic therapy were excluded from the 5-day analysis but included in the day-by-day and survival analyses up to the point of withdrawal.

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Table 1. Patients' demographics

	Granisetron	Alizapride/ dexamethasone
No. of patients	103	94
Sex (M/F)	81/22	74/20
Mean age [years(S.D.)]	50.15 (15.51)	48.22 (16.27)
Cytostatic therapy* [mean dose (S.D.) mg/m²]		
Cisplatin	74	68
	20.40 (0.51)	19.60 (0.50)
Ifosfamide	29	25
	1565.19 (9.49)	1619.06 (8.51)
Etoposide	—	1
	—	128.36 (0)

*Additional cytostatics given in combination with these 3 main regimens were well balanced across the two antiemetic treatment groups.

Table 2. Efficacy criteria

Complete responder	No vomiting and/or mild nausea
Major responder	1 vomit and/or moderate to severe nausea
Minor responder	2–4 vomits
Failure	>4 vomits

Vomit = retch.

Missing efficacy assessments

For efficacy assessments missing because of reasons other than withdrawal: if the patient was asleep it was assumed that no nausea/vomiting was present; if two or more consecutive assessments were missing it was assumed that there was nausea and vomiting; if a single assessment was missing an assumption was made based on the flanking data—if this was conflicting, the worse case was assumed (nausea and vomiting present).

Analysis

Statistical analysis was performed with either the χ^2 test or the Cox log rank test. The χ^2 test was used for the analysis of cross-classifications of two grouping-type variables: in testing for differences between the two treatment groups for proportions of patients who were complete responders, who had good or very good global efficacy assessments, who had adverse events or who had worse appetite over 5 days.

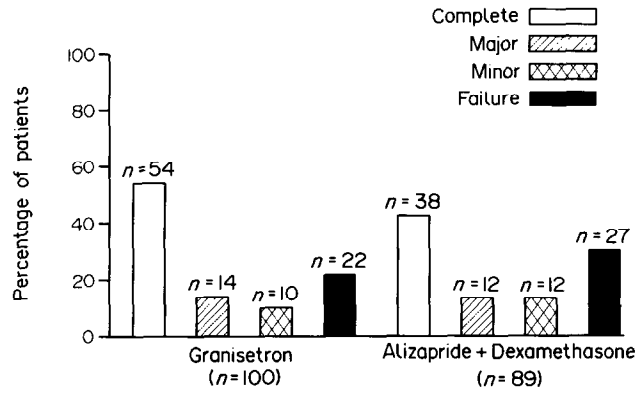

Fig. 2. Response rates over 5 days.

The Cox log rank test was used for the analysis of differences in survival curve distributions: in testing for differences in time to the first episode of vomiting, the first episode of nausea, the first episode of moderate/severe nausea, less than complete response, use of additional study medication or use of any rescue therapy. In all cases, a 2-tailed significance level of 5% was used to determine whether the result was to be regarded as statistically significant.

RESULTS

200 patients were randomised into the trial, 104 to receive granisetron and 96 to receive alizapride/dexamethasone. One of the patients was randomised to receive granisetron and two were randomised to receive comparator medication did not receive therapy; thus the number of patients who were treated were 103 and 94, respectively. Patients' demographics are shown in Table 1.

Efficacy

The efficacy criteria used in this study are defined in Table 2. In the analysis of complete response over 5 days, 3 patients were dropped from the granisetron group and 5 from the comparator group, according to the criteria listed above. Thus the numbers of patients analysed were 100 (granisetron) and 89 (comparator). The number of complete responders over the 5 days of chemotherapy was 54/100 in the granistron group (54.0%) and 38/89 in the comparator group (42.7%). A further breakdown of patient response over the 5 days into complete/major/minor responder or failure is shown in Fig. 2. There was no significant difference between treatment groups in the number of patients who were complete responders or major responders and those who were minor responders or failures.

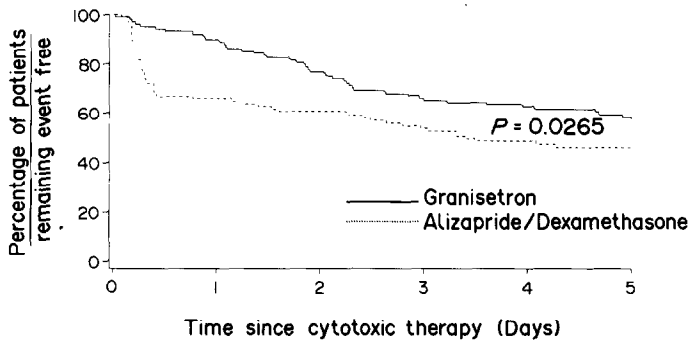

Fig. 3. Time to less than complete response during study period (5 days).

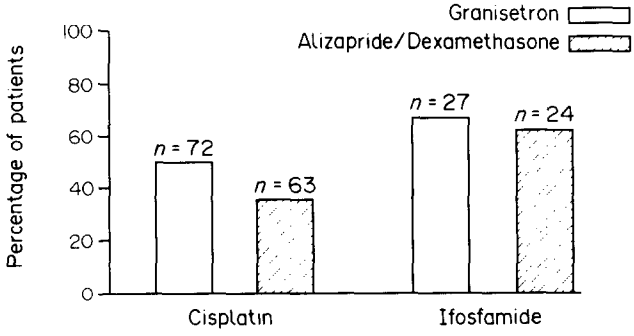

Fig. 4. Complete response over 5 days by cytotoxic group.

The time to less than a complete response over the 5-day treatment period is shown in Fig. 3. Patients receiving granisetron maintained a complete response for a significantly longer period than those receiving the comparator medication ($P = 0.0265$).

The patient response over 5 days broken down by cytostatic group is shown in Fig. 4. This shows that granisetron had more complete responders than alizapride/dexamethasone in cisplatin-treated patients (49.3% vs. 35.4%), while there was a smaller difference between the two treatments in those patients receiving ifosfamide (66.7% vs. 62.5%). (Since only a single patient in the alizapride/dexamethasone group received etoposide, the results of the study cannot be taken as typical of those for etoposide patients; thus the combined ifosfamide patients and single etoposide-treated patient are referred to as ifosfamide-treated patients throughout the text.)

An analysis of the complete response day-by-day showed a significantly higher number of complete responders in the granisetron group on day 1: 93/103 (90.3%) vs. 60/91 (65.9%) for the comparator group ($P < 0.001$). There was no significant difference between the two antiemetic treatments on days 2–5. The survival time to the first episode of moderate or severe nausea is shown in Fig. 5. Patients receiving granisetron did not experience moderate/severe nausea for a significantly longer period than those in the comparator group ($P = 0.0349$). It was found that a single 40 μg/kg dose of granisetron, given prior to chemotherapy, was the only antiemetic treatment required by the majority of patients (Table 3).

Adverse events

There were significantly fewer adverse events in the granisetron group than with the comparator (47.6% vs. 61.7%) as shown in Table 4 ($P = 0.047$). Significantly more patients receiving granisetron suffered from constipation (10.7% vs. 3.2%)($P = 0.04$). None of the patients receiving granisetron suffered from extrapyramidal effects, compared with 5.3% of those receiving alizapride/dexamethasone ($P = 0.02$).

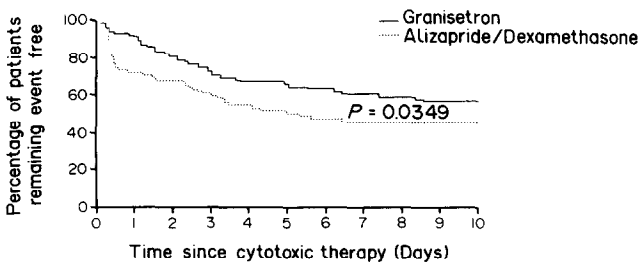

Fig. 5. Survival time to first moderate or severe nausea episode during study period.

Table 3. Number of granisetron doses which patients received in each 24-h period

Day	No. of doses 1 (%)	2 (%)	3 (%)
1	94	3	3
2	93	5	2
3	88	7	5
4	85	10	5
5	87	7	6

DISCUSSION

The complete response rate for granisetron over 5 days was greater than that of the comparator (54.0% vs. 42.7%). In addition there were fewer failures in the granisetron group (22.0% vs. 30.3%). These results show that for 5-day cycles of chemotherapy, granisetron is numerically superior to a combination of alizapride and dexamethasone.

While granisetron is numerically superior to the comparator medication in terms of efficacy, it also offers advantages because of its ease of administration. The alizapride/dexamethasone treatment requires at least four separate injections or infusions over each 24-h period, and up to six if rescue doses are given. This treatment is further complicated if it is necessary to decrease sequentially the dose of alizapride due to unwanted side-effects (see Introduction).

A single dose of granisetron (40 μg/kg) given prior to chemotherapy was the only antiemetic treatment required by most patients (>85%), and of those who received a second or third dose, they generally responded well and their symptoms resolved. It has been reported before that granisetron administered intravenously normally rescues patients experiencing nausea/vomiting within minutues [5].

The efficacy results by cytotoxic group (Fig. 4) show that for patients receiving cisplatin there were more complete responders in the granisetron group than for the comparator (49.3% vs. 35.4%). While this was also true for patients receiving ifosfamide/etoposide, the difference between groups was much less marked (66.7% vs. 62.5%).

Alizapride is a new substituted benzamide with properties similar to those of metoclopramide [1]. While its properties as a dopamine D_2 antagonist have resulted in it being effective against the moderately emetogenic cytotoxic drugs, alizapride offers only weak protection against the severe forms of emesis evoked by drugs such as cisplatin [8]. The dopamine D_2 receptor

Table 4. Adverse events

	Granisetron	Alizapride/ dexamethasone	P
Total number	103(100)	94(100)	
Number with events	49 (47.6)	58 (61.7)	0.047
Leukopenia	12 (11.7)	15 (16.0)	N.S.
Constipation	11 (10.7)	3 (3.2)	0.041
Fever	8 (7.8)	4 (4.3)	N.S.
Headache	7 (6.8)	2 (2.1)	N.S.
Extrapyramidal effects	0 (0)	5 (5.3)	0.02

N.S. = not significant.
Percentages in parentheses.

antagonist domperidone has little or no ability to prevent cisplatin-evoked emesis in ferrets [9], so presumably any efficacy seen with alizapride (at high doses) results from 5-HT_3 antagonist actions.

In contrast, granisetron is a specific 5-HT_3 receptor antagonist. It has been suggested that 5-HT_3 receptor antagonism might prevent the emesis evoked by cisplatin and moderately emetogenic cytostatic drugs [8]. This may explain the differences in complete responder rates seen between the two treatments in cisplatin-induced emesis but not in moderately emetogenic ifosfamide.

Patients receiving granisetron had a significantly longer ($P = 0.0349$) survival time to the first episode of moderate/severe nausea than those in the comparator group. Since nausea is often more of a problem than emesis in patients receiving chemotherapy, this is another advantage of using granisetron as an antiemetic.

Patients treated with granisetron experienced significantly fewer adverse events than those treated with alizapride/dexamethasone (47.6% vs. 61.7%) ($P = 0.047$). The adverse events seen in this study are typical of those that might be expected for granisetron in that constipation (10.7%) is a recognised side-effect of the drug which slows large bowel transit time. The frequency of this side-effect is equivalent to that reported in 24-h studies [10]. Extrapyramidal effects (which are often seen with high-dose dopamine antagonists) [3, 11] were not seen with granisetron. The incidence of headache (6.8%) in the granisetron group is lower than has typically been reported in previous granisetron studies (usually being reported as approximately 15%) [10, 12–14]. It is encouraging to find a lower incidence of headache in this 5-day study than has been observed in single-day studies of patients [14]. The headaches were generally mild and responded well to analgesics such as paracetamol.

In the comparator group there was a 5.3% incidence of extrapyramidal effects. This is an expected side-effect of high-dose dopamine antagonists such as alizapride, particularly when administered on consecutive days [3]. Other adverse effects which might be expected in patients treated with alizapride—such as drowsiness, muscle spasm, hypotension and cardiovascular disturbances [15, 16]—were not among the more common adverse events noted in this study (although they were reported by a few patients).

The incidence of fever was higher in the granisetron group than in the comparator group, and this was clinically (although not statistically) significant. Fever is a relatively common occurrence in cancer patients; it may result from tumour necrosis, inflammation, transfusions and drugs (including both chemotherapeutic and antimicrobial agents) [17]. It is possible that the incidence of fever in the comparator group was lower because the febrile response was masked by the steroid (dexamethasone) which the patients in this group received.

A similar incidence of leukopenia was noted in both treatment groups (11.7% for granisetron and 16.0% for comparator); this is probably of no clinical significance in relation to the antiemetics since leukopenia is a recognised side-effect of chemotherapy [18].

In summary, granisetron is superior to a combination of alizapride and dexamethasone in preventing nausea ($P < 0.04$) and vomiting over 5 consecutive days (55% vs. 44% complete responders). The dosage regimen with granisetron is much more convenient than the comparator medication, with a single intravenous administration being the only treatment required by the vast majority of patients. The incidence of adverse events is significantly lower with granisetron than with the comparator ($P < 0.05$), and the serious extrapyramidal effects seen with alizapride were not seen with granisetron. Granisetron appears to be a convenient and safe antiemetic which is at least as effective as alizapride/dexamethasone in patients receiving fractionated chemotherapy over 5 days.

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