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Clinical paper

Granisetron plus methylprednisolone for the control of high-dose cisplatin-induced emesis

J-P Kleisbauer, C García-Girón,[1] M Antimi,[2] MC Azevedo,[3] H Balmes,[4] B Massuti-Sureda,[5] A Contu,[6] A Luque[7] and P Pellier[8]

Hopital Sainte-Marguerite, Marseille, France. [1]Hospital General Yagüe, Burgos, Spain. [2]Ospedale S Eugenio, Roma, Italy. [3]Institutio Portugues Oncologia Francisco Gentil, Oporto, Portugal. [4]CH Gaston Doumergue, Nimes, France. [5]Hospital General de Alicante, Alicante, Spain. [6]Ospedale Civil, Sassari, Italy. [7]SmithKline Beecham Pharmaceuticals, Madrid, Spain. [8]SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK. Tel: (+44) 1279 622000; Fax: (+44) 1279 646038.

This double-blind, double-dummy, randomized study compared the 24 h efficacy and safety of granisetron alone (3 mg i.v. over 30 s) or in combination with methylprednisolone (250 mg i.v. twice daily) in preventing nausea and vomiting in 308 patients (254 males) receiving high-dose cisplatin (100 mg/m^2 or above) for mainly lung, and head and neck cancers. All patients received oral follow-on therapy comprising oral granisetron and methylprednisolone during the following 6 days. Primary efficacy variables were the proportions of complete responses (CR; no vomiting, no worse than mild nausea, no rescue and no withdrawal), no vomiting and no nausea over the first 24 h following initiation of the cisplatin infusion. The two treatment groups were well matched for demographics, cancer site, cisplatin dose and duration of infusion. Granisetron plus methylprednisolone was significantly more effective than granisetron alone for all primary efficacy variables: CR 78 versus 59% ($p<0.001$), no vomiting 80 versus 61% ($p<0.001$) and no nausea 74 versus 57% ($p<0.002$). Significantly more patients receiving the combination were free of any emetic symptoms (74 versus 54%, $p<0.001$). Significantly fewer patients receiving combination therapy also required rescue therapy with i.v. granisetron (12.2 versus 21.7%, $p=0.026$). During the follow-on period, complete response rates varied day by day from 50 to 71%. Both treatments were well tolerated, with constipation, abdominal pain and headache as the most frequent adverse events. [© 1998 Lippincott-Raven Publishers.]

Key words: Cisplatin, efficacy, emesis, granisetron, granisetron plus methylprednisolone, safety.

Introduction

Nausea and vomiting are some of the most well-known and feared side-effects of cancer therapy, using either cytotoxic drugs or irradiation. These symptoms present a major problem for both patients and oncologists. Although not usually life threatening in adults, they may result in physical damage to the patient, caused by dehydration, malnutrition, fractures and laceration of the esophagus.[1] Furthermore, they often severely compromise patients' well being and contribute significantly to non-compliance with these potentially life-saving therapies.[2] It is therefore important that emetogenic chemotherapy regimens are combined with the use of effective antiemetics.

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist that has demonstrated good antiemetic efficacy against both cytotoxic drugs[3,4] and emesis produced by irradiation.[5] Studies have shown that it is at least as effective as the conventional antiemetic therapies,[6–8] has a more convenient dosing schedule[4] and is not associated with extrapyramidal side-effects.[3,4,6] Moreover, it has shown at least equivalent efficacy to other 5-HT$_3$ antagonists (ondansetron and tropisetron)[9–11] and, in cross-over studies, a majority of patients have expressed a preference for granisetron over these other two agents.[10,11] Nevertheless, a minority of patients do not respond satisfactorily to therapy with granisetron or other 5-HT$_3$ antagonists. In particular, all antiemetics are less effective against highly emetogenic regimens such as high-dose cisplatin therapy.

Corticosteroids have been shown to be effective antiemetics against chemotherapy-induced nausea and vomiting.[12,13] Moreover, recent studies have reported that corticosteroids can enhance the antiemetic efficacy of 5-HT$_3$ antagonists. Thus, the combination of granisetron and dexamethasone has greater anti-

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Correspondence to P Pellier

emetic efficacy than granisetron alone against either moderately emetogenic[14] or highly emetogenic (cisplatin) chemotherapy.[15] Likewise, combination treatments with ondansetron plus dexamethasone[16] and ondansetron plus methylprednisolone[17] have been shown to be more effective than the 5-HT_3 antagonist alone.

The results reported here are of a randomized, double-blind study in which the combination treatment of granisetron plus methylprednisolone was compared with granisetron alone in patients receiving highly emetogenic, high-dose cisplatin chemotherapy. The two treatments were compared during the first 24 h after chemotherapy. After this, open-label treatment with the combination was given to all patients for a further 6 days, in order to prevent the delayed nausea and vomiting that are associated with cisplatin chemotherapy.

Materials and methods

Patients

The patients recruited were adults of either sex who were chemotherapy naive and scheduled to receive cisplatin at a dose of at least 100 mg/m^2. All patients had a performance status of 2 or less (World Health Organization classification) and gave their informed consent to enter the trial.

Drug treatment

The trial was randomized and double blind. During the first 24 h of treatment (day 0), both granisetron and methylprednisolone were given i.v. Granisetron, 3 mg in 10 ml sterile saline, was injected over 30 s, ending 5 min before cisplatin therapy began. If breakthrough symptoms of nausea and vomiting occurred, rescue therapy with granisetron, either i.v. or i.m. (3 mg in 1 ml injected into gluteal muscle), could be administered. Up to two additional doses of granisetron could be given as rescue medication, with at least 10 min between the doses. If these additional doses did not provide adequate control of nausea and vomiting, the patient was withdrawn from the trial and given alternative antiemetics at the discretion of the physician.

Methylprednisolone and its placebo, 250 mg of powder in 100 ml diluent, was administered in a 20 min infusion, ending 10 min before cisplatin therapy started. An identical infusion was made at the end of the infusion of cisplatin.

On days 1-6, open-label oral granisetron and methylprednisolone were administered to all patients to prevent delayed emesis. The dose of granisetron was 1 mg twice daily. The twice-daily doses of methylprednisolone were as follows: on days 1 and 2, 32 mg; on days 3 and 4, 16 mg; and on days 5 and 6, 8 mg.

Cisplatin chemotherapy was administered at a dose of at least 100 mg/m^2 in an infusion lasting not more than 4 h. Other cytostatics given included cyclophosphamide, etoposide, doxorubicin, epirubicin and fluorouracil. All of these drugs were given after cisplatin and no emetogenic agents were given after the first day of treatment.

Study protocol

For the first 24 h after the start of cisplatin therapy the patient was treated in hospital. Every 6 h during that time, the worst severity of nausea and the number of episodes of vomiting during the previous time period were recorded. After the first 24 h, patients were discharged with a supply of oral antiemetics and a diary card for them to record daily assessments of the worst severity of nausea and the number of episodes of vomiting they experienced. Patients returned to the clinic for a follow-up assessment 7-11 days after the start of treatment. At follow-up, the diary cards and any unused medication were returned—the latter was used to assess patient compliance with the oral antiemetic medication. In addition, reports of any adverse events during the study period were elicited by asking the neutral question 'Do you feel different in any way since starting the treatment or since the last visit?'. The safety of antiemetic treatment was also assessed by recording vital signs and laboratory parameters before and after treatment.

Assessment of efficacy

The primary efficacy variables were the proportions of patients experiencing a complete response, no vomiting or no nausea during the first 24 h. Complete response was defined as no more than mild nausea, no vomiting, no need for rescue medication and no withdrawal from the study.

Secondary variables were as follows: the proportion of patients who experienced total control (no nausea, no vomiting, no need for rescue medication and no withdrawal) in the first 24 h; the proportions of patients who experienced a complete response, no nausea, no vomiting or total control over the 7 days of

the trial; the times recorded between the onset of chemotherapy and the first episode of vomiting, or first use of rescue therapy, in the first 24 h; the proportion of patients who received rescue therapy with granisetron.

Statistics

It was planned to recruit 300 patients, in order to allow detection of a 20% difference between treatment groups on a bilateral test at the 0.05 level of significance with at least 90% power. Comparisons of the proportions of patients experiencing a complete response, no nausea, no vomiting and total control of vomiting were made using the χ^2 test, unless the sample size was low, in which case, Fisher's exact test (two-tailed) was used. Interactions between treatment effects and other factors were analyzed by logistic regression.

Results

Patient demographics

A total of 308 patients were recruited in the intention-to-treat population. The granisetron treatment group comprised 152 patients, whereas the granisetron plus methylprednisolone group had 156 patients; 143 and 142 patients in these groups, respectively, completed 7 days' evaluation. The most common disease sites were lung, head and neck, and ovary. The demographics of the intention-to-treat population are shown in Table 1.

The mean dose of cisplatin administered was 104.7 mg/m^2 in the granisetron group and 106.3 mg/m^2 in the granisetron plus methylprednisolone group.

Treatment efficacy

The proportions of patients who showed a complete response, no vomiting, no nausea or total control during the first 24 h are shown in Figure 1. Higher proportions of patients receiving the combination treatment of granisetron plus methylprednisolone showed an antiemetic response to treatment (77.6 versus 58.6% for complete response, 79.5 versus 60.5% for no vomiting, 74.4 versus 57.2% for no nausea). The differences between the treatment groups were significant for all three parameters: $p<0.001$ for complete response and no vomiting, $p=0.002$ for no nausea. These treatment differences were mirrored by a significant difference in the proportion of patients who experienced total control (no nausea, no vomiting and no need for rescue medication) in the first 24 h; 73.7% of patients receiving combination treatment compared with 52.6% of those receiving granisetron alone ($p<0.001$).

Regression analysis showed significant interactions between the treatment effects, and patients' sex, age and alcohol consumption (Table 2). Male patients showed a better response to treatment than females: the complete response rate was 65.9% in men and 23.1% in women who received granisetron alone, and 82.8 and 53.6%, respectively, in men and women who received the combination treatment ($p<0.01$). Likewise, significant interactions were found for the parameters of no nausea and no vomiting. In addition,

Table 1. Demographic characteristics of the intention-to-treat population

Characteristic	Treatment group	
	Granisetron	Granisetron plus methylprednisolone
No. of patients	152	156
male [*n* (%)]	126 (82.9)	128 (82.1)
female [*n* (%)]	26 (17.1)	28 (17.9)
Age		
mean ± SD (years)	57.2 ± 10.2	57.2 ± 11.7
range (years)	22–74	17–76
Disease site		
lung [*n* (%)]	81 (53.3)	83 (53.2)
head and neck [*n* (%)]	41 (27.0)	34 (21.8)
ovary [*n* (%)]	8 (5.3)	6 (3.8)
Mean dose of cisplatin (mg/m^2)	104.7	106.3
Infusion rate (mg/m^2/min)	1.21	1.25

patients older than 65 years showed a greater complete antiemetic response (64.1% for granisetron and 80.9% for granisetron plus methylprednisolone) than those who were younger than 45 years (52.9 and 60.0%, respectively; $p<0.01$). Again, the same pattern of results was found for the measurements of no vomiting and no nausea. Logistic regression also suggested an association between patients' alcohol consumption and their antiemetic response ($p=0.053$)—the highest complete response rate was found in patients who reported an alcohol consumption of more than 20 units per week.

Of the 308 patients included in the study, 22 and 30 received one or two additional doses of granisetron, respectively. Significantly fewer patients receiving the combination treatment required rescue medication (12.2% of those receiving combination versus 21.7% receiving granisetron alone, $p=0.026$). In most patients the rescue medication was given for more than two episodes of vomiting. Only 15 patients (4.9%) withdrew from the study because of antiemetic efficacy. Survival analysis of the time to the first episode of vomiting and to use of rescue medication also confirmed the superiority of the combination regimen over granisetron alone (Figure 2).

During the follow-up period of days 1-6 (when all patients were receiving both granisetron and methylprednisolone) the therapeutic advantage observed with the combination treatment on day 0 was reduced, so there were no differences between the treatment groups for this period. The complete response rates over days 1-6 ranged from 59 to 71% for the group that had received combination treatment and from 50 to 71% for the group that had received granisetron. In both groups the highest complete response rate occurred on day 4 and the lowest on day 1. Approximately 30% of patients experienced a complete response throughout the whole treatment and follow-up period.

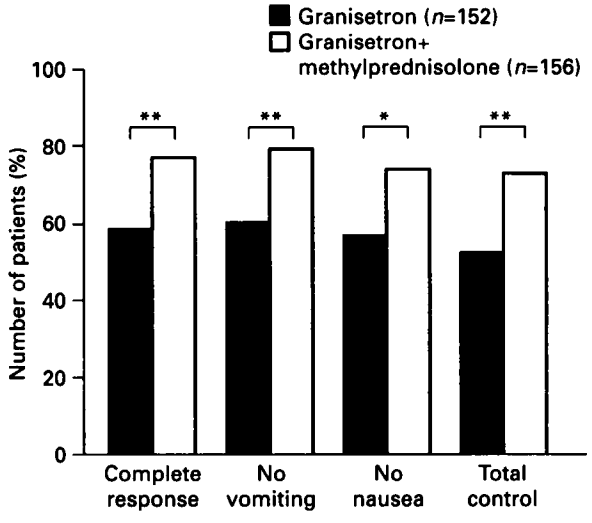

Figure 1. The proportions of patients who experienced a complete response, no vomiting, no nausea and total control during the first 24 h after cisplatin therapy started. $^{**}p<0.001$, $^{*}p<0.002$.

Table 2. Complete response rates by gender, age and alcohol consumption and treatment group

	Granisetron	Granisetron plus methylprednisolone
Gender		
male	83/126 (65.9%)	106/128 (82.8%)
female	6/26 (23.1%)	15/28 (53.6%)
Age (years)		
<45	9/17 (52.9%)	12/20 (60.0%)
>65	25/39 (64.1%)	38/47 (80.9%)
Alcohol consumption (units/week)		
<10	43/82 (52.4%)	54/77 (70.1%)
⩾10	45/65 (69.2%)	60/71 (84.5%)

Treatment safety

The overall incidence of adverse events did not differ between the treatment groups—75.7% of the granisetron group and 69.9% of the combination treatment group experienced at least one adverse event. The most frequent adverse events in both groups were constipation (20%), abdominal pain (10.7%) and head-

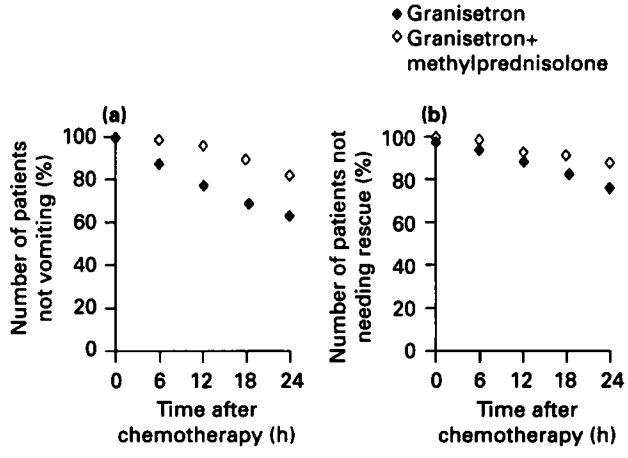

Figure 2. Proportions of patients (Kaplan–Meier estimates) who were free of vomiting (a) or required no rescue medication (b) in the first 24 h.

ache (8.8%). Only 10 patients (3.2%) withdrew because of adverse experiences. One serious adverse event, anaphylactoid shock and cardiac arrest, was attributed to the administration of methylprednisolone; it resolved without sequelae. No other adverse events were considered attributable to the antiemetic medications.

A total of 10 patients died during the course of the study and follow-up (one patient died 30 days after receiving study medication). None of the deaths were considered to be related to the study medication.

All changes in vital signs were small and not clinically significant. Changes in laboratory values were reported as adverse events in 34 patients in the granisetron group (22.4%) and 22 patients in the combination treatment group (14%). The most frequently reported events were increased non-protein nitrogen (8.6% for granisetron, 1.9% for combination treatment), increased blood urea nitrogen (5.9 and 2.6%) and leucopenia (4.6 and 3.8%).

Discussion

Both of the treatments used in this study were highly effective against acute emesis; the treatment effects were particularly good given the high dose of cisplatin that was used in these patients. The complete response rate achieved in the group of patients receiving granisetron alone was similar to those reported from other trials using highly emetogenic chemotherapy.[18,19] Moreover, this response rate was improved significantly by the addition of methylprednisolone to the treatment regimen—the overall complete response rate increased from 54 to 78%. This result supports those that have shown that dexamethasone can enhance the effect of granisetron against both moderately emetogenic[14] and high-dose cisplatin[15] chemotherapy, and that both methylprednisolone[17] and dexamethasone[16] enhance the effects of ondansetron and tropisetron.[20] The beneficial effects of the combination treatment were particularly evident in the female patients, in whom the complete response rate more than doubled from 23.1 to 53.6%.

Efficacy of the oral treatment regimen against delayed emesis was also good—the daily complete response rate for the whole treatment period was between 50 and 70%.

The adverse events reported by patients in this study were similar to those reported in previous trials of granisetron[3-5] and other 5-HT_3 antagonists.[10,11] The good safety profile of granisetron was almost unaffected by the addition of methylprednisolone to the treatment regimen.

In conclusion, the combination treatment of granisetron and methylprednisolone produced a greater antiemetic effect than granisetron alone against highly emetogenic chemotherapy. This combination treatment should prove particularly useful in situations where there is a high risk of emesis, e.g. in patients receiving high-dose cisplatin chemotherapy or in female patients. Nevertheless, the antiemetic responses to delayed emesis were not as good as those of the acute symptoms, thus this problem requires further research to define the optimal treatment regimen.

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