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Antiemetic efficacy of granisetron in patients with gynecological malignancies

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The efficacy and tolerability of granisetron in the management of acute and delayed emesis was compared with that of a multiple antiemetic drug combination regimen, including metoclopramide, dexamethasone, lorazepam and orphenadrine. The trial was a randomized, cross-over study involving 111 patients with gynecological cancers undergoing chemotherapy with cisplatin. Granisetron was significantly more effective than the combination regimen during the first 24 h after chemotherapy; complete response rates were 67 and 48%, respectively ($p = 0.002$). There was a significant reduction in the effectiveness of the combination during the second treatment cycle, compared with the first. In contrast, the efficacy of granisetron did not differ between the two cycles. The response rate during the 6 days after chemotherapy was 40.8% in both groups. At the end of the study, 55% of patients preferred granisetron and 23% preferred the combination ($p < 0.001$). Granisetron was well tolerated. The principal adverse event was headache, which was reported in 7% of patients. The results of this study confirm that granisetron is effective in the treatment of cisplatin-induced nausea and vomiting during the 24 h after chemotherapy.

Key words: Antiemetic treatment, cisplatin, granisetron, patient preference.

Introduction

Granisetron is a selective 5-HT_3 antagonist that has been shown to be effective in the prophylaxis and treatment of chemotherapy-induced nausea and vomiting. In dose-ranging studies and placebo-controlled trials, a 3 mg dose of granisetron produced complete control of vomiting and nausea over 24 h in 44–92% of patients receiving highly or moderately emetogenic chemotherapy.[1–4] Other studies have shown that granisetron is as effective in the acute treatment of nausea and vomiting as combination treatment with metoclopramide and dexamethasone,[5] or metoclopramide, dexamethasone and diphenhydramine.[6] In addition, granisetron has been shown to be more effective than the combinations of chlorpromazine and dexamethasone[7] or prochlorperazine and dexamethasone.[8] Comparisons with regimens containing metoclopramide have shown that granisetron does not produce the extrapyramidal effects sometimes seen with the latter drug.[5,6]

Delayed nausea and vomiting, which may persist for several days, is a common problem with chemotherapy regimens containing cisplatin. Treatment with oral granisetron, 1 mg b.d., for 7 days after moderately emetogenic chemotherapy has been reported to produce complete control of nausea and vomiting in 59% of patients.[9] There is evidence that delayed emesis is best controlled by controlling symptoms during the initial 24 h after chemotherapy; Carmichael *et al.*, for example, found that the addition of dexamethasone enhanced the efficacy of granisetron, both during the acute phase and during the 7 days after moderately emetogenic chemotherapy.[10] By contrast, studies with the 5-HT_3 antagonist ondansetron have yielded variable results; in one study, there was no significant difference between ondansetron and metoclopramide in the control of delayed emesis,[11] while Jones *et al.* reported that ondansetron was significantly less effective in the prevention of delayed nausea than dexamethasone in this situation.[12]

This paper reports the results of a study carried out to investigate the effectiveness of granisetron in the prophylaxis and control of acute and delayed nausea and vomiting in patients with gynecological malignancies, who were treated with cisplatin. Granisetron was compared with a conventional antiemetic 'cocktail' regimen consisting of metoclopramide dexamethasone, lorazepam and orphenadrine.

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Patients and methods

The study was a randomized, single-blind, cross-over trial conducted at 14 centers in Italy. The patients were women with gynecological malignancies and a WHO performance status score of 2 or less, who had not previously received chemotherapy. Patients were excluded from the study if they had marked renal or hepatic dysfunction, congestive heart failure (New York Heart Association classes III or IV), acute nausea or vomiting within the preceding week, peptic ulceration or gastric compression. Chemotherapy consisted of cisplatin (mean dose 60 mg/m^2, range 46–90 mg/m^2), given for at least two cycles.

Prior to chemotherapy, patients were randomized to receive antiemetic treatment with granisetron or a multiple antiemetic drug combination regimen. The granisetron regimen consisted of a 3 mg dose given by i.v. infusion 10 min before chemotherapy, followed by maintenance treatment with 1 mg given orally 6 and 12 h after chemotherapy, and hence twice daily for 6 days. The patients who received the combination regimen were given metoclopramide, 2 mg/kg i.v., 30 min before, and 1 and 1.5 h after chemotherapy, dexamethasone (20 mg i.v.) 40 min before chemotherapy, lorazepam (2.5 mg orally) 1 h before chemotherapy, and orphenadrine (40 mg i.m.) 35 min before chemotherapy; metoclopramide, 10 mg t.d.s. orally, was then given for 6 days, starting 24 h after the start of cisplatin treatment. Rescue medication with alternative antiemetics was given if necessary. The alternative antiemetic regimen was given during the second chemotherapy treatment cycle.

The principal measures of efficacy were the proportion of complete responses (defined as complete freedom from vomiting and no more than mild nausea, no rescue therapy, and no withdrawal from the trial) over the initial 24 h, the proportion of complete responses over the subsequent 6 days and patient preferences for treatment at the end of the treatment cycle. Secondary measures included the number of patients in whom total control of nausea and vomiting was achieved over the 7 day period, the number of patients in whom either nausea or vomiting was controlled over the same period and the time to nausea or vomiting or use of rescue medication (time to less than complete response).

Patients were treated as inpatients during the 24 h after chemotherapy and the severity of nausea or vomiting were assessed every 6 h. Nausea was scored as 'none', 'mild', 'moderate' or 'severe'. Vomiting was recorded on a scale of 'none', 'one episode of vomiting' (defined as a productive vomit or retch), 'two episodes', 'three episodes', 'four episodes' or 'more than four episodes'. The times of the first moderate or severe nausea and vomiting were also recorded. The patients' level of arousal and subjective assessment of appetite were monitored every 6 h; heart rate, blood pressure and body temperature were measured at the same times. At the end of the initial 24 h period, the investigators provided a global assessment on a five-point scale, ranging from 'very good' to 'very poor'. Nausea and vomiting during the subsequent 6 days were recorded by the patients on diary cards. Follow-up assessments were made 7 days after chemotherapy. The second treatment cycle started 20 days after initial chemotherapy.

Blood and urine samples were taken for standard laboratory tests before the start of chemotherapy and 7 days after chemotherapy in both cycles. Adverse events were recorded throughout the study period.

The proportion of complete responses in both treatment groups were compared by means of the Mainland–Gart test and Prescott's test.[13,14]

The study was carried out in accordance with the Declaration of Helsinki and approved by local ethics committees.

Results

It was calculated that a sample size of 100 patients (50 in each group) would be necessary to show a statistically significant 28% difference between the treatment groups, with a study power of 80%. This calculation assumed a complete response rate of 50% in the group receiving the metoclopramide combination regimen.

A total of 111 patients were enrolled into the study. Of these, 13 were excluded from the analysis: 10 never entered the second treatment cycle, one received granisetron in both cycles and assessments were incomplete in two cases. The demographic characteristics of the patients are shown in Table 1. The majority of patients (61.2%) were between 45 and 64 years of age and 24.5% were aged 65 years or over. Most patients (79.6%) had cancer of the ovary and 94.9% had WHO performance ratings of 0 or 1. The majority (93%) consumed less than 10 units of alcohol per day; thus, this was a population at high risk of emesis as there is evidence that emesis is more difficult to control in women[15] and in low alcohol consumers.[16] Of the 101 patients who entered the second treatment cycle, 98 were assessed at the 7 day follow-up.

Table 1. Patient characteristics

Patient characteristics	Number (%)
Mean age (years)	57.7
Age range (years)	25–79
Alcohol consumption	
< 10 units/day	91 (92.9)
10–20 units/day	6 (6.1)
> 20 units/day	1 (1.0)
Primary disease site	
ovary	78 (79.6)
cervix	5 (5.1)
other	14 (14.3)
missing	1 (1.0)

Primary efficacy measures

The proportion of complete responses during the 24 h after chemotherapy was significantly ($p = 0.002$) higher among patients treated with granisetron than among patients receiving the combination regimen. Overall, 66 patients (67%) showed a complete response during granisetron treatment, compared with 47 (48%) during treatment with the combination regimen (Figure 1) ($p = 0.002$). There was no evidence of any carry-over effect between the two treatment cycles. There was, however, a significant ($p = 0.048$) difference between the cycles, which was mainly due to a 20% reduction in the response to the combination regimen. During the first cycle, 27 patients (57%) showed a complete response to the combination, compared with 20 (39%) during the second cycle (Figure 1). The response rate among granisetron-treated patients was similar in both cycles (Figure 1).

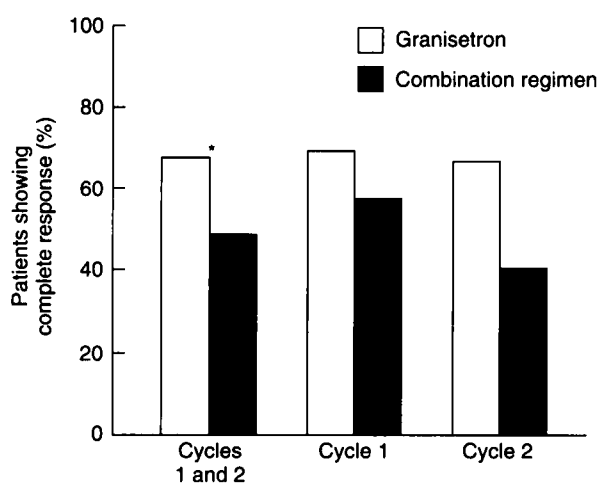

Figure 1. Proportions of complete responses during the first 24 h after chemotherapy. $^*p = 0.002$, granisetron versus metoclopramide-containing combination.

The complete response rate during the 6 days after chemotherapy was 40.8% with both treatments (Figure 2); there was no evidence for any cycle effect. The response rates for both treatments were comparable on each day, except for the first day after discharge from hospital. Complete response rates on this day were 61% with granisetron and 47% with the combination.

The number of complete responses during the 7 day treatment period was similar with each treatment (36% with granisetron and 31% with the combination). No overall treatment differences were observed.

At the end of the study, more patients expressed a preference for granisetron than for the combination regimen (Figure 3). Overall, 54 patients (55%) preferred granisetron, compared with 23 (23%) who preferred the combination ($p < 0.001$). Similarly, the

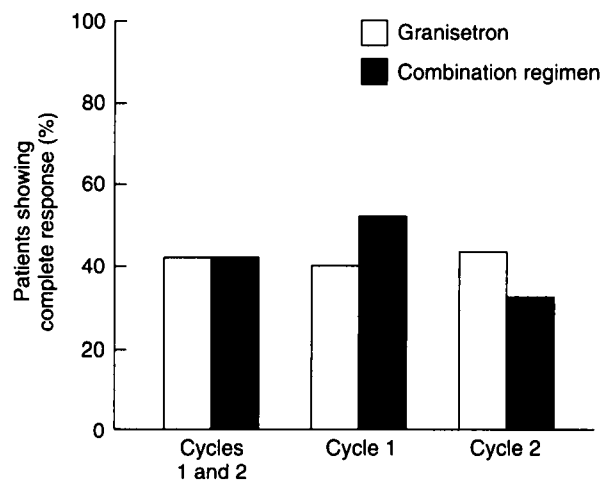

Figure 2. Proportions of complete responses during day 2–7 after chemotherapy, i.e. after discharge from hospital.

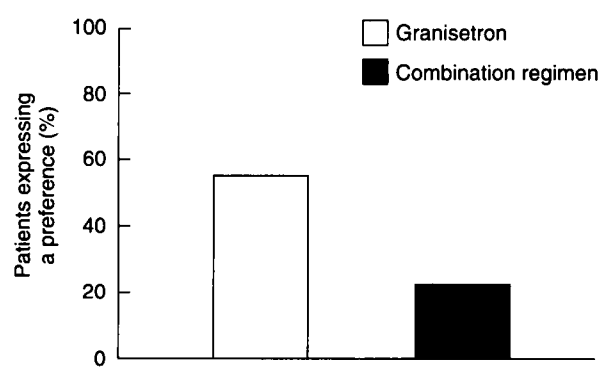

Figure 3. Patient preferences for granisetron or the metoclopramide-containing combination regimen. Significantly more patients expressed a preference for granisetron than for the combination regimen ($p < 0.001$).

investigators rated granisetron as more effective in 69 patients (70%) and the combination regimen more effective in 14 patients (14%). Again, this difference was highly significant ($p < 0.001$).

Secondary efficacy measures

During the initial 24 h, total control of nausea and vomiting was achieved in 44 patients (45%) during granisetron treatment and 38 patients (39%) during treatment with the antiemetic combination. This difference was not statistically significant. Over 7 days, total control was achieved in 10 granisetron-treated patients and 12 patients treated with the combination; again, this difference was not significant. The same was true when the responses for days 1–3 and 4–6 were compared. There was, however, a significant ($p < 0.001$) cycle effect between days 4 and 6, when the response to treatment with the combination regimen decreased from 64% during the first cycle to 29% during the second cycle. Similar trends were seen for the control of nausea.

Granisetron was significantly more effective than the combination regimen in controlling vomiting during the first 24 h; control was achieved in 67 (68%) granisetron-treated patients, compared with 52 (53%) of patients given the antiemetic combination ($p = 0.008$). The effects of both treatments were similar over the 7 day treatment period.

Granisetron significantly prolonged the time to less than complete response (Figure 4). The difference between the two treatments was most marked during the first 12 h, but was maintained throughout the study. There were no significant differences between the treatments in the time to first nausea or vomiting episode.

The global efficacy of granisetron was judged by the investigator to be 'good' or 'very good' in 85 patients (86%) during granisetron treatment, compared with 62 (63%) patients during treatment with the combination regimen.

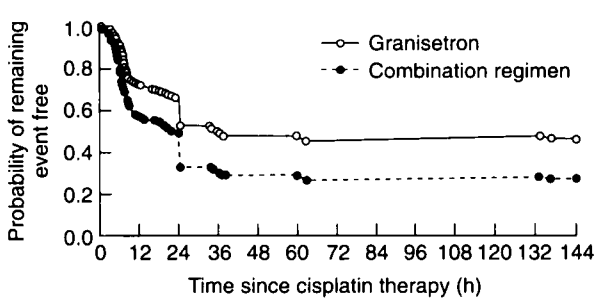

Figure 4. Probability of remaining event free over 7 days, confirming better survival on granisetron throughout the period of observation ($p = 0.039$).

The patients' assessments of appetite were similar with both treatments. Appetite declined markedly after cisplatin treatment; 29 granisetron-treated patients (39%) had a worse appetite than in the previous week, compared with 35 (36%) of patients given the combination treatment. This figure decreased to approximately 10% in both groups by the end of the 7 day treatment period.

Drowsiness was more common during treatment with the combination regimen than during granisetron treatment; 6 h after cisplatin, 82% of patients treated with the combination were drowsy, compared with 14% of granisetron-treated patients. At any time during the initial 24 h, fewer patients treated with granisetron were asleep than patients given the combination regimen.

Tolerability

There were no significant changes in heart rate, blood pressure or body temperature with either treatment. Adverse events were reported by 50 patients (51%) during granisetron treatment and 46 patients (47%) during treatment with the combination regimen. These were mainly mild and well tolerated. Leucopenia was reported in 20% of patients during both treatments; this was presumably attributable to cisplatin treatment. Other than leucopenia, the most common adverse events were headache in the case of granisetron (7%) and somnolence in the case of the combination regimen (5%).

One patient died after one cycle of treatment. The cause of death was recorded as pulmonary embolism, which was not considered to be related to treatment.

Discussion

The results of this trial show that granisetron is more effective than a conventional antiemetic combination regimen during the first 24 h after chemotherapy with cisplatin. There was, however, no difference between the two treatments during the subsequent 6 days. The patients could be regarded as being at high risk of experiencing emesis, as emesis is more difficult to control in women, and in patients whose use of alcohol is low.

The response rates obtained with granisetron during the 24 h after chemotherapy are comparable

to those seen in other studies.[5,6,17] In one previous comparison with metoclopramide, for example, a 40 mg/kg dose of granisetron (approximately equivalent to the 3 mg dose used in this study) produced complete responses in 70% of patients, compared with 67% in patients receiving a combination of metoclopramide and dexamethasone.[5]

The finding that there was no significant difference between the two treatments during the 7 days after chemotherapy is also consistent with previous studies. Heron *et al.* found no significant difference between granisetron and metoclopramide in controlling emesis over 7 days after cisplatin chemotherapy.[18] The complete response rate with granisetron alone reported by these authors was 16.8%; the corresponding figure in the present study was 36%. The results of these studies suggest that delayed emesis is best controlled by controlling symptoms during the initial 24 h after chemotherapy, a finding consistent with those of Carmichael *et al.*[10]

While complete response rates appeared to be similar during the two granisetron cycles, the response rate declined markedly during treatment with the combination regimen, from 57.4% in the first cycle to 39.2% in the second. No treatment–cycle interaction was observed, and thus the difference in response rate between granisetron and the conventional combination regimen represents a genuine difference in efficacy. Analysis of the time to less than complete response showed that the early difference between the two treatments, which became apparent during the first 12 h, was maintained during treatment (Figure 4). Thus, granisetron significantly delayed the onset of moderate or severe nausea or vomiting and the need for rescue medication.

Both patients and investigators expressed a significant preference for granisetron over the combination regimen. Again, this is consistent with previous studies.[19,20] In cross-over comparisons with other 5-HT_3 receptor antagonists, approximately 40% of patients preferred granisetron.[19,20]

The strong preference for granisetron, even though no difference in efficacy was apparent during the delayed phase, might reflect the fact that nausea and vomiting are most severe during the 24 h after chemotherapy. Hence, patients' preferences may be based on the superior antiemetic control provided by granisetron during the acute phase.

Granisetron was well tolerated in this study. As in other trials,[5,6,17] headache was the most common adverse event. Somnolence was more common during treatment with the combination regimen than during granisetron treatment; no extrapyramidal symptoms were recorded in either group.

In conclusion, this study has confirmed the efficacy of granisetron in controlling nausea and vomiting during the 24 h after chemotherapy with cisplatin. The finding that granisetron and the conventional antiemetic combination regimen were of comparable efficacy during the delayed phase is consistent with the experience of De Mulder *et al.* with ondansetron.[11] By contrast, Jones *et al.* showed that ondansetron was significantly less effective than dexamethasone in controlling delayed nausea.[12] The efficacy of granisetron in this group of high-risk patients is reflected in the preference for granisetron over the conventional antiemetic combination reported by both patients and clinicians.

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