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Report

A double-blind randomized study comparing intramuscular (i.m.) granisetron with i.m. granisetron plus dexamethasone in the prevention of delayed emesis induced by cisplatin

The Italian Multicenter Study Group

Granisetron has been shown to exert a beneficial therapeutic effect in the prophylaxis and treatment of acute nausea and vomiting due to chemotherapy. However, limited data regarding its efficacy in the prevention and treatment of delayed emesis are available. A total of 532 patients entered this multicenter double-blind study, aimed at comparing the efficacy and safety of intramuscular (i.m.) granisetron with that of i.m. granisetron plus dexamethasone. Complete response and total control were evaluated for 3 days following the first 24 h after cisplatin administration in two groups of patients: 262 treated with granisetron 3 mg i.m. daily (plus placebo), and 265 with granisetron at the same dose plus dexamethasone 8 and 4 mg twice daily. The rate of complete response was 58.0% in the granisetron group and 78.9% in the granisetron plus dexamethasone group over days 1–3 ($p<0.01$). Similarly, over the same period total control was 44.7% with granisetron alone and 65.3% with granisetron plus dexamethasone ($p<0.01$). Local and systemic tolerability of the i.m. therapy with granisetron were satisfactory. In conclusion, granisetron plus dexamethasone showed good protection against delayed emesis due to emetogenic chemotherapy. [© 1999 Lippincott Williams & Wilkins.]

Key words: Cisplatin, dexamethasone, granisetron, nausea, vomiting.

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Introduction

Nausea and vomiting are still included among the most distressing adverse effects of cancer chemotherapy. They can even severely exacerbate a patient's condition by causing dehydration, malnutrition and physical damage, such as laceration of the esophagus. Moreover, the induced discomfort can affect patient compliance with cytotoxic therapy.

Among the chemotherapy agents, cisplatin is the most emetogenic, with an effect at high doses lasting for up to 1 week. The phenomenon of acute emesis occurs in the first 24 h after cytotoxic treatment. Afterwards, the nausea and vomiting episodes of the following days are defined as delayed emesis and are registered in up to 90% of patients.[1,2]

Effective antiemetic measures in patients receiving cancer chemotherapy are now included in the standard care. Several new serotonin antagonists (e.g. ondansetron, granisetron, dolasetron and tropisetron)

are now available in clinical practice or in trials. However, the adequate control of delayed emesis is still the subject of many investigations. Moreover, other factors that affect antiemetic efficacy, such as previous experience of acute vomiting, female gender and cisplatin dose, have to be taken into account.

Single therapy with metoclopramide or dexamethasone has been shown to be as effective as placebo in cisplatin-induced delayed emesis.[3] Investigation of combination therapy of steroids and 5-HT_3 antagonists in the control of delayed emesis has been limited and the results conflicting. A study by Latreille *et al.* found no significant benefit of the oral administration of dexamethasone plus granisetron versus dexamethasone plus placebo on delayed emesis.[4] Conversely, based on a review of evidence from clinical trials, Kris *et al.* recommend a combination of a dexamethasone with either metoclopramide or a specific 5-HT_3 antagonist as the treatment of choice in preventing delayed emesis.[5] Combination therapy of metoclopramide plus dexamethasone has been shown to be effective in preventing delayed emesis in 52% of patients.[2] However, the adverse events associated with the use of metoclopramide, including extrapyramidal effects, diarrhoea, fatigue, sedation, lethargy and drowsiness, are well recognized.[6] The continued investigation of clinical strategies to prevent delayed emesis is thus necessary to determine efficacy and assess best available therapy.

Antiemetic therapy with the new selective 5-HT_3 receptor antagonist, granisetron, has been successfully investigated in the control of acute emesis with intravenous (i.v.) or intramuscular (i.m.) preparations.[7-9] The combination with a steroid has proved to further enhance its efficacy.[10] It is therefore interesting to investigate the effect of the i.m. granisetron treatment in the prevention of delayed emesis. Intramuscular injection of granisetron is also a convenient way of administration for cancer out-patients, in whom the oral route may be inappropriate and the i.v. administration distressing.

This paper presents the results of the first trial on the use of i.m. granisetron compared with i.m. granisetron plus dexamethasone in the control of cisplatin-induced delayed emesis.

Materials and methods

Patients

Patients were recruited from 45 centers in Italy. At least 500 patients (250 in each treatment group) were required in order to detect a difference of at least 14% (90% power, two-tailed test at 5% level, based on 30% baseline response rate). Male and female patients were included provided they: were at least 18 years old, were chemotherapy naive, were scheduled to receive cisplatin on a single day in a dose of 50-120 mg/m^2 (alone or in combination with other cytotoxic agents) and had a Karnofsky performance rate of over 40.

Patients were excluded from the trial if, after the first 24 h and until the follow-up visit, they were scheduled to receive any other cytotoxic agent, with the exclusion of etoposide, teniposide, vincristine or 5-fluorouracil. Other exclusion criteria were: severe concomitant illness or other possible causes of vomiting, concomitant abdominal radiotherapy, treatment with corticosteroids (unless given as physiological supplement), benzodiazepines or other antiemetics, experience of vomiting or severe nausea within the previous week, leukopenia or thrombocytopenia, participation to any other trial within the previous 3 months.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee for each center. Written informed consent was obtained from each patient.

Drug administration

On the day of chemotherapy treatment (day 0), a standard i.v. therapy of granisetron (3 mg/3 ml) combined with dexamethasone phosphate (20 mg) was given to all patients included in the study, immediately before cisplatin administration. All patients were then randomized to i.m. treatment of either granisetron plus placebo or granisetron plus dexamethasone. These treatments were aimed at preventing delayed emesis, and commenced 24 h after cisplatin administration and continued for 3 days at the following doses: day 1-2, granisetron 3 mg once daily plus dexamethasone 8 mg (or placebo) twice daily; day 3, granisetron 3 mg once daily plus dexamethasone 4 mg (or placebo) twice daily. If these drug regimens were ineffective and a patient experienced three or more episodes of vomiting and/or severe nausea, rescue medication was allowed on the chemotherapy day: i.v. granisetron for in-patients (not more than two 3 mg administrations) and i.m. dexamethasone for out-patients (not more than two 8 mg administrations). During the following 3 days the adopted rescue medication was prochlorperazine suppository 10 mg (not more than two suppositories a day). If this medication did not control the symptoms of nausea and vomiting, the patient could be with-

drawn from the study and given an alternative antiemetic treatment of the investigator's choice.

Assessment of efficacy

On the chemotherapy day, the assessment of nausea and vomiting following administration of cisplatin was made at 1, 2, 6, 12, 18 and 24 h in order to evaluate emesis conditions during the acute phase. During the following 3 days, each patient registered the number of emetic episodes or retches and the intensity of nausea on a diary card. The assessment of nausea was recorded as none, mild, moderate or severe. Time 0 was considered to be 24 h after cisplatin administration and delayed emesis evaluation commenced at this time.

A complete response was defined as no vomiting and no more than mild nausea, no need of rescue medication, and no withdrawal from the study over the 3 days of treatment. An absolute absence of nausea and/or vomiting, no need of rescue medication, and no withdrawal from the study were considered as total control. Nausea or vomiting control were defined as the absence of nausea or vomiting. All these items were recorded by the patient on a diary card.

Intention-to-treat (ITT) analysis was performed on all patients treated with at least one i.m. granisetron dose. Efficacy evaluable (EE) analysis was applied to all patients who completed the study. The primary efficacy variable was the number of patients showing a complete response over days 1-3. This outcome had to be adjusted for the initial response after the assessment of the status on day 0. The secondary efficacy parameters in this study were: total control over days 1-3 (ITT population); vomiting control over days 1-3 (ITT population); nausea control over days 1-3 (ITT population); time to less than complete response, less than total control, first episode of vomiting, first episode of nausea, first use of rescue medication over days 1-3 (ITT population). These parameters were also evaluated on a daily basis. In addition, complete response and total control over days 1-3 or on a daily basis were considered for the EE population.

All patients attended the clinic for a follow-up visit 9 ± 3 days after the end of treatment. At this time the out-patients returned their diary cards.

Assessment of safety

Any adverse events occurring during a patient's stay in hospital were recorded by the investigator. At the follow-up clinic visit, reports of adverse events were elicited by the neutral question: 'Do you feel different in any way since starting the treatment or since the last visit?'. Patient withdrawals and relevant reasons were also reported.

Statistical evaluation

All frequencies of efficacy variables were compared between groups with the χ^2 test. The Cox log-rank test was used to compare differences in 'time to event' variable distributions over days 1, 2 and 3, as indicated in the secondary efficacy definition. The influence of prognostic factors and of the status at day 0 were analyzed by means of the logistic regression.

Results

Patient demography

A total of 532 patients entered the study, of whom five were excluded from the ITT analysis for different reasons (no assumption of at least one i.m. dose or missing information on this), leaving 262 patients receiving granisetron, and 265 taking granisetron and dexamethasone. A further 13 patients were excluded from the EE analysis due to withdrawal for lack of efficacy, adverse events or protocol violations, there were therefore 251 granisetron-treated patients, and 263 taking granisetron and dexamethasone in this population.

In the ITT population the mean age was 60.31 years and 66.5% of the patients were male. All patients were Caucasian, with the lung being the primary site of disease in 45.9%. Mean body weight was 67.5 kg and the mean cisplatin dose was 80.6 mg/m^2, administered in a mean time of 75.4 min.

Antiemetic efficacy

The comparison between groups at baseline showed homogeneity in all prognostic factors (alcohol consumption, Karnofsky scale, emesis during pregnancy, travel sickness and rescue medication consumption at day 0), except the response to acute therapy on day 0 ($p < 0.01$). The overall percentage of complete response on day 0 was 82.7%; when evaluated retrospectively, this figure was 77.9% in patients who were later randomized to granisetron alone and 87.5% in patients who were later randomized to receive granisetron plus dexamethasone.

The rate of complete response to i.m. treatment in the granisetron group (58.0%) was significantly different ($p < 0.01$) from that of the granisetron plus dexamethasone group (78.9%) over days 1-3 (Figure 1). Daily frequency figures showed a similar pattern (Figure 1).

To adjust the assessment of the i.m. treatment for response on day 0 and for any prognostic factor, the logistic regression was used. This analysis showed that the overall difference between the two groups (days 1-3) remained significant ($p < 0.01$). However, the difference between the declining response in both groups on days 1-3 versus day 0 was within 10% (Table 1).

Table 2 compares, on days 1-3, the percentage of complete response in all patients with the percentage of those patients who were complete responders on day 0. Overall, patients who showed a response on day 0 experienced higher response rates than those who did not. The number of complete responders increased in both groups on days 1-3, but there was a significant difference ($p < 0.01$) between the groups in those patients who were complete responders on day 0. In contrast, in those patients who were not complete responders on day 0, the difference between groups was significant ($p < 0.05$) only on day 1.

A similar difference is found between groups in rates of total control: 44.7% of patients treated with granisetron had a total control over days 1-3 compared with 65.3% of the granisetron plus dexamethasone group ($p < 0.01$). Rates over the whole observation period and on a daily basis are shown in

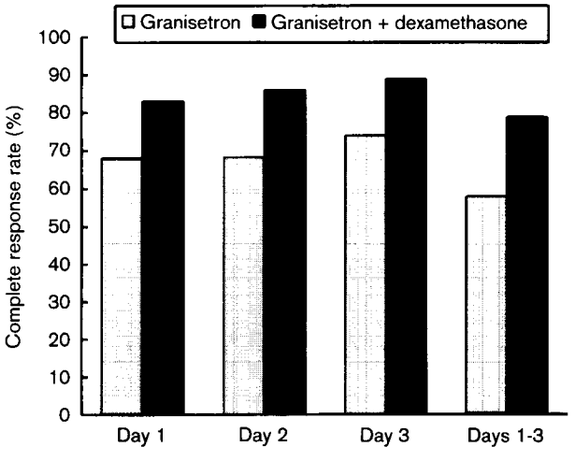

Figure 1. Complete response rates (%) over days 1–3 for the ITT population.

Table 1. Declining response in both groups on days 1–3 versus day 0

Day	Granisetron (%)	Granisetron plus dexamethasone (%)	Difference (%)
1	−10.68	−4.15	6.53
2	−9.92	−1.51	8.41
3	−3.05	1.51	4.56

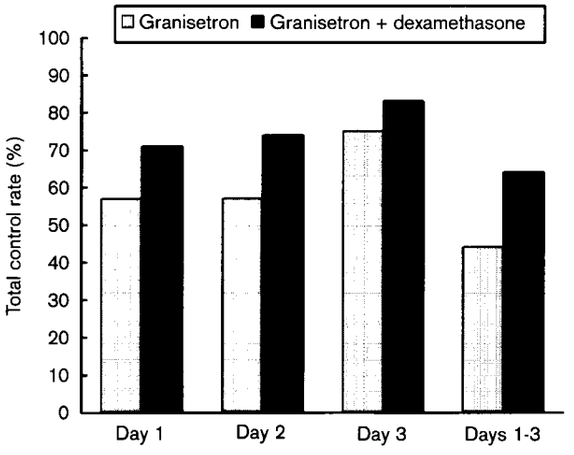

Figure 2. Total control rates (%) over days 1–3 for the ITT population.

Table 2. Complete response on days 1–3 in all patients compared with those who were complete responders on day 0

Days	Granisetron		Granisetron plus dexamethasone	
	All patients (%)	Complete responders day 0 (%)	All patients (%)	Complete responders day 0 (%)
1	67.18	79.41	83.40	88.79
2	67.94	75.49	86.04	90.52
3	74.81	80.88	89.06	92.67
1–3	58.02	68.14	78.87	84.48

Figure 2. The same relationship with the status at day 0 is noticeable.

The total absence of day-by-day nausea or vomiting confirms a statistically higher efficacy of the combination therapy (Table 3).

Other secondary efficacy parameters showed greater efficacy with the combination compared with granisetron alone (time to less than complete response, time to less than total control) or a greater efficacy for granisetron alone compared with the combination (time to first nausea episode, time to first vomiting episode and time to first use of rescue). Relevant mean values by group are summarized in Table 4.

The comparison between groups in the EE analysis showed the same results for complete response and total control, as for the ITT analysis.

Evaluation of safety

Local and systemic tolerability was satisfactory. Local reactions, which were transient and resolved spontaneously, were observed in 11 patients treated with granisetron, five patients treated with dexamethasone and 30 patients treated with placebo (sterile water for injection, not containing any of those components for injectable preparation likely to affect local tolerability).

Table 3. Percentage of nausea control and vomiting control in both groups

Symptom	Day	Granisetron (%)	Granisetron plus dexamethasone (%)
Nausea	1	66.03	74.72
	2	64.89	78.11
	3	75.19	87.17
	1–3	51.15	68.68
Vomiting	1	72.14	86.79
	2	74.81	90.57
	3	81.68	92.45
	1–3	62.21	83.02

Discussion

The results of this study indicate that the i.m. administration of granisetron was well tolerated and confirm that the control of acute emesis confers better protection from delayed emesis. A high response rate for acute emesis control has been observed on day 0; this may be in part explained by the fact that all patients received i.v. dexamethasone for acute emesis control, in addition to granisetron. Complete responses obtained with i.m. granisetron alone during the delayed phase (days 1, 2 and 3) ranged from 67 to 74%, but an advantage was seen when granisetron was combined with dexamethasone (range 83–89%).

The absence of a third control group, receiving no granisetron at all, excludes the possibility to discriminate the effect attributable to granisetron itself in this study. Evidence is conflicting on the benefit of continuing 5-HT_3 antagonists after acute control of emesis and further placebo-controlled trials are required.[4,5]

A direct comparison with other recognized antiemetic therapies, such as the dexamethasone plus metoclopramide combination, would have completed the evaluation of the absolute effect of i.m. granisetron against delayed emesis. However, multiple comparisons on more than two treatment arms are very difficult to perform in a large multicenter double-blind setting.

Conclusion

Granisetron combined with dexamethasone showed good protection against delayed emesis due to highly emetogenic chemotherapy. The activity of single i.m. granisetron treatment requires further investigation.

Table 4. Mean values of time to less than complete response, time to less than total control, time to the first nausea episode, time to the first vomiting episode and time to the first use of rescue medication in both groups

Parameter	Granisetron	Granisetron plus dexamethasone
Time to less than complete response (h)	17.55	19.64
Time to less than total control (h)	17.69	20.33
Time to first nausea episode (h)	25.58	24.93
Time to first vomiting episode (h)	18.00	16.64
Time to first use of rescue medication (days)	0.58	0.29

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