Anti-Cancer Drugs 1995, **6**, pp. 652–656

A comparison of the antiemetic efficacy and safety of intramuscular and intravenous formulations of granisetron in patients receiving moderately emetogenic chemotherapy

A Contu,[1] N Olmeo,[1] S Piro,[1] R Sabbatini,[2] R Depenni,[2] V Silingardi,[2] A Zaniboni,[3] F Meriggi,[3] D Donati,[4] A Maestri,[4] S Tateo,[5] A Carpi,[6] E Campora,[7] B Coria,[8] E Riva[9] and P Barbieri[9]

[1]Medical Oncology, Hospital of Sassari, Sassari, Italy. [2]Medical Oncology Department, University of Modena, Modena, Italy. [3]Medical Oncology, Spedali Civili, Brescia, Italy. [4]Medical Oncology, Arcispedale S Anna, Ferrara, Italy. [5]Gynaecology Institute, University of Pavia, Pavia, Italy. [6]Medical Oncology, Hospital of Piacenza, Piacenza, Italy. [7]Medical Oncology, Ist Naz Ricerca sul Cancro, Genova, Italy. [8]Medical Oncology, Presidio Ospedaliero ULSS 8, Vicenza, Italy. [9]Medical Department, SmithKline Beecham Italy, Milan, Italy.

A total of 120 patients were treated with granisetron either intramuscular (i.m.) or intravenous (i.v.) in a cross-over design, over two successive cycles of moderately emetogenic chemotherapy. Of the 117 patients evaluable for efficacy, 74.4% receiving i.m. and 76.9% receiving i.v. treatment experienced a complete response (no vomiting, no more than mild nausea, no need for rescue medication and no study withdrawal in the 24 h following the onset of chemotherapy). Only a small proportion of the patients experienced any vomiting, either during the first 24 h or in the follow-up period of 4–10 days. There were no statistically significant differences in any of the efficacy parameters between the two routes of administration of granisetron. Both formulations of granisetron were also equally well tolerated. The main treatment-related adverse effects were headache and constipation (experienced by 13–15% of patients); local reactions to i.m. injection of granisetron were experienced by 2.6% of patients.

Key words: Antiemetic, granisetron, intramuscular.

Introduction

Nausea and vomiting are some of the most well known and feared side-effects of cancer chemotherapy, and present a major problem for both patients and oncologists. These symptoms may result in physical damage to, or even the death of, the patient, caused by dehydration, malnutrition, fractures and laceration of the oesophagus.[1] Furthermore, they often severely compromise patients' well being and are a significant reason for 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-HT_3 antagonist that has demonstrated good antiemetic efficacy.[3,4] Studies have shown that it is at least as effective as the conventional antiemetic therapies,[5–7] has a more convenient dosing schedule[4] and is not associated with extrapyramidal side-effects.[3–5] Moreover, it has shown equivalent efficacy to other 5-HT_3 antagonists (ondansetron and tropisetron),[8–10] and in crossover studies, a majority of patients have expressed a preference for granisetron over these other two agents.[9,10]

Studies published to date have all tested the intravenous (i.v.)[3,4] or oral[11,12] formulations of granisetron. However, in some situations, there could be clinical advantages for formulations administered by other routes (e.g. in the outpatient setting, for post-operative nausea and vomiting, and in children, in whom veins can be difficult to locate). A study of the effects of i.v., oral, subcutaneous and intramuscular (i.m.) formulations of granisetron in preventing nausea and vomiting in ferrets showed that its antiemetic efficacy was maintained, regardless of the route of administration.[13] A pharmacokinetic trial in 20 healthy volunteers showed that systemic delivery of granisetron was slower for i.m. than i.v. administration (SmithKline Beecham, unpublished results). Nevertheless, all other pharmacokinetic parameters were equivalent for the two routes of administration and the treatment was equally well tolerated for both formulations.

This is therefore the first report of a trial of the i.m. formulation of granisetron in patients receiving cancer chemotherapy. The study was a multicenter,

Correspondence to P Barbieri, Medical Department, SmithKline Beecham, Via Zambeletti, 20021 Baranzate di Bollate, Milan, Italy. Tel: (+39) 2-3806-3245; Fax: (+39) 2-3806-3003

open, crossover trial that tested the efficacy and safety of single 3 mg doses of i.m. and i.v. granisetron (Kytril®; SmithKline Beecham, Harlow, UK), in preventing nausea and vomiting induced by moderately emetogenic chemotherapy.

Materials and methods

Patients

Patients were recruited at eight centers in Italy. At least 112 patients needed to be recruited, in order to give a statistical power of 80% to detect a 15% difference in response rates produced by the two formulations. The patients were at least 18 years old, chemotherapy naive and scheduled to receive at least two cycles of one or more of the drugs shown in Table 1. Patients were excluded if they were scheduled to receive dacarbazine, cisplatin, cytarabine, ifosfamide or meclorethamine, or if they were to receive any chemotherapy after day 1 of the cycle, with the exception of etoposide, teniposide, vincristine or 5-fluorouracil (5-FU). Other exclusion criteria were: severe concomitant illness or other possible causes of vomiting, concomitant radiotherapy, treatment with corticosteroids, benzodiazepines or other antiemetics, experience of vomiting or severe nausea within the previous week, leukopenia or thrombocytopenia, and receipt of an investigational new drug within the previous 3 months. Written or oral witnessed informed consent was obtained from each patient.

At the start of the study, patients were randomized in the crossover design to receive granisetron, either i.m. on cycle 1 and i.v. on cycle 2 or vice versa.

Drug administration

Granisetron for i.m. injection was supplied as 3 mg in 1 ml of injection medium. The dose was injected 15 min before the start of chemotherapy. Granisetron for i.v. infusion was supplied as a 3 mg/3 ml ampoule. The 3 ml was further diluted in 0.9% saline to give 20 ml of infusion medium, which was administered over 5 min, finishing 15 min before the onset of chemotherapy.

Should these doses of antiemetic medication prove ineffective and a patient experience three episodes of vomiting or severe nausea within 24 h of the onset of chemotherapy, rescue medication could be administered. For inpatients, rescue medication was an i.m. injection of granisetron, 3 mg. For outpatients it was dexamethasone, 8 mg, i.m., which could be repeated after 12 h if required. If rescue medication did not control the symptoms of nausea and vomiting, the patient was withdrawn from the study and given alternative antiemetic medication of the investigator's choice.

Table 1. Moderately emetogenic cytostatic agents that were administered to patients in the study

Agent	Dose
Cyclophosphamide	≥ 600 mg/m^2 to 1 g/m^2
Doxorubicin	≥ 50 mg/m^2
Epidoxorubicin	≥ 75 mg/m^2
Carboplatin	≥ 300 mg/m^2

Assessment of efficacy

All patients were observed for 6 h following the onset of chemotherapy. After 6 h outpatients were discharged with a diary card for recording efficacy parameters, whereas inpatients were observed for another 18 h. The primary efficacy variable was the number of patients showing a complete response to treatment. This parameter was recorded both for the first 24 h overall, and for set time intervals of 0–1, 1–2, 2–6, 6–12, 12–18 and 18–24 h within that period—the incidence of nausea and vomiting in each of those intervals was recorded, regardless of whether patients suffered these symptoms in previous or subsequent intervals. A complete response was defined as no vomiting and no more than mild nausea, no requirement for rescue medication, and no withdrawal from the study. Secondary efficacy variables were the times between the onset of chemotherapy and the first experience of vomiting and nausea, and the number of patients who required rescue medication. Patients all attended the clinic for a follow-up visit between 4 and 10 (7 ± 3) days after treatment. At that time, outpatients returned their diary cards, and all patients reported the incidence of nausea and vomiting in the period between discharge and follow-up.

Assessment of safety

Any adverse events that occurred during a patient's stay in hospital were noted by the investigator. At the follow-up clinic visits, 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 were all reported, along with the reason for withdrawal.

Statistical evaluation of results

No carry-over effects of treatment were found between cycles 1 and 2, so the crossover study design was accepted. The primary efficacy variables and the numbers of patients requiring rescue medication were all analyzed and compared across treatment groups using the χ^2 test. The times before onset of nausea and vomiting were compared using Student's *t*-test.

Results

Patient demographics

A total of 120 patients were recruited to the trial in the intention-to-treat group. Of these, three were not evaluable for treatment efficacy, leaving a total of 117 patients. Demographic data for this group are shown in Table 2. Most of the patients were women (85%) and the main disease was breast cancer (71%). The most common chemotherapy regimens were: CMF (cyclophosphamide, methotrexate, 5-FU; 45.8% of patients), FEC (5-FU, epirubicin, cyclophosphamide; 10.8%) and carboplatin plus etoposide (8.3%).

Antiemetic efficacy

In the first 24 h after the start of chemotherapy, complete responses were experienced by 74.4% of the patients receiving i.m. granisetron and 76.9% given i.v. treatment. There was no statistical difference between these response rates. Complete response rates in set time intervals after the onset of chemotherapy decreased from 100% in the first hour to just over 80% at 18–24 h (Figure 1). Again, no significant differences were found in the responses of the two treatment groups.

The percentages of patients experiencing no nausea and vomiting, both in the first 24 h and during the follow-up period of 4–10 days, are shown in Figure 2. It can be seen that only a small proportion of patients experienced any vomiting, whereas a larger proportion experienced some nausea. The mean times between the start of chemotherapy and the onset of vomiting were 11.1 and 11.3 h for i.m. and i.v. granisetron, respectively. The corresponding mean times for nausea were 8.2 and 8.9 h, respectively. None of the numerical differences between treatment formulations reached statistical significance.

Table 2. Demographic data for the patients evaluable for efficacy

Characteristic	Value
Male/female (%)	18/102 (15/85)
Mean age ± SD (years)	57.2 ± 11.6
range	28–81
Main disease site; *n* (%)	
breast	85 (70.8)
lung	13 (10.9)
ovary	4 (3.3)
soft-tissue sarcoma	1 (0.8)
other	17 (14.2)

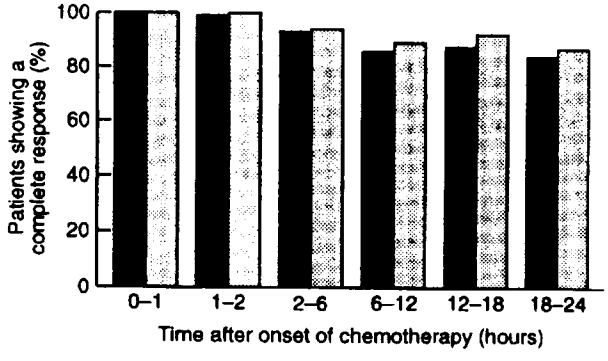

Figure 1. The percentages of patients who experienced complete responses during set time intervals in the first 24 h after the onset of chemotherapy. ■, i.m.; ▨, i.v.

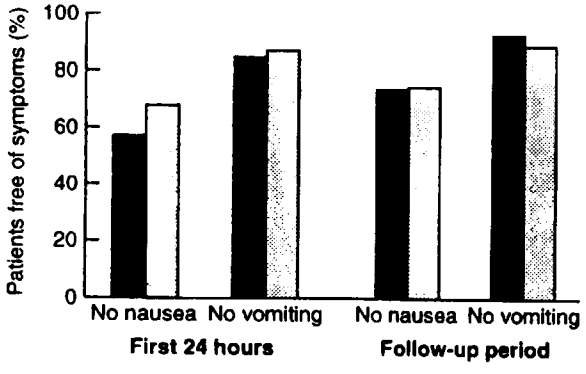

Figure 2. The percentages of patients who experienced no nausea and no vomiting during the first 24 h after the onset of chemotherapy and during the follow-up period of 4–10 days. ■, i.m.; ▨, i.v.

Table 3. The most commonly experienced adverse events (reported by at least 5% of patients)

Adverse event	Treatment group	
	i.m. ($n=94$)	i.v. ($n=98$)
Asthenia	8 (8.5%)	6 (6.1%)
Constipation	14 (14.9%)	13 (13.3%)
Headache	14 (14.9%)	13 (13.3%)
Leukopenia[a]	22 (23.4%)	24 (24.5%)
Any event	44 (47.1%)	49 (50.4%)

[a] Never related to granisetron treatment

A total of 13 patients (11.1%) required rescue medication with either i.m. granisetron or dexamethasone: eight of the patients (6.8%) were receiving i.m. granisetron and five patients (4.3%) receiving i.v. treatment. Only one patient in the intention-to-treat population was withdrawn from the study because of lack of antiemetic efficacy.

Evaluation of safety

A total of 47.1% of patients receiving i.m. granisetron and 50.4% receiving i.v. treatment experienced adverse events. The most common of these events (those reported by at least 5% of patients) are shown in Table 3. Most of the adverse events (58.5% in the i.m. group and 61.2% in the i.v. group) were not considered to be related to the study medication (e.g. leukopenia).

Local reactions to the i.m. injection of granisetron were found in only three patients (2.6%). These reactions were: pain that lasted for 6 h, hematoma at the follow-up visit and redness at the end of the first 24 h, which had improved at the follow-up 6 days later.

Three patients in the intention-to-treat group were withdrawn from the study. One, mentioned above, was withdrawn because of lack of antiemetic efficacy. Another died from progressive disease, and a third died after experiencing hematemesis and melaena, which were not considered to be related to granisetron treatment.

Discussion

Both the i.m. and i.v. formulations of granisetron were highly effective in preventing nausea and vomiting. Despite the fact that the patient group comprised mainly women and was therefore a high-risk group for emesis, only small proportions of the patients experienced vomiting, either in the first 24 h after treatment or during the follow-up period. The complete response rates produced by granisetron treatment compared favorably with those previously observed in trials with both moderately emetogenic chemotherapy,[8,9,14,15] and with cisplatin- and ifosfamide-based chemotherapies.[10,16,17] The response rates were also similar to those obtained using ondansetron against moderately emetogenic chemotherapy regimens.[18,19]

There were no significant differences between the antiemetic efficacies of the i.m. and i.v. formulations—a result that is consistent with those obtained in the studies of animals and healthy volunteers.[13]

Granisetron was well tolerated by the patients, regardless of the route of administration. Headache and constipation are the only two adverse events that are consistently associated with this treatment. Headache is generally only mild or moderate in severity, and of short duration. No patient experienced any of the extrapyramidal symptoms that are sometimes associated with conventional antiemetics and can be highly distressing to patients. Granisetron produced local reactions to i.m. injection in only a small proportion of patients and, again, these reactions were mild and of short duration.

Conclusion

Granisetron administered by an i.m. route is as effective and well tolerated as the i.v. formulation. The introduction of this new formulation should increase the flexibility of use of this drug, both in conjunction with chemotherapy and in other indications, e.g. as rescue antiemetic therapy or in the treatment of radiotherapy-induced emesis in outpatients.

Acknowledgments

The authors would like to thank Dr O Mariani for her careful management of the study and Dr G Serra for the accurate statistical analysis performed.

References

1. Laszlo J. Emesis as limiting toxicity in cancer chemotherapy. In: Laszlo J, ed. *Antiemetics and cancer chemotherapy*. Baltimore: Williams and Wilkins 1983: 1–5.

2. Schmitt R. Quality of life issues in lung cancer. New symptom management strategies. *Chest* 1993; **103** (Suppl): 51S–5S.
3. Soukoup M. Clinical experience with intravenous granisetron. *Anti-Cancer Drugs* 1994; **5**: 281–6.
4. Tabona MV. An overview on the use of granisetron in the treatment of emesis associated with cytostatic chemotherapy. *Eur J Cancer* 1990; **26** (Suppl 1): S37–41.
5. Chevallier B on behalf of the Granisetron Study Group. Efficacy and safety of granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. *Eur J Cancer* 1990; **26** (Suppl 1): S33–6.
6. Marty M on behalf of the Granisetron Study Group. A comparison of granisetron as a single agent with conventional combination antiemetic therapies in the treatment of cytostatic-induced emesis. *Eur J Cancer* 1992; **28A** (Suppl 1): S12–16.
7. Warr D, Willan A, Finse S, *et al.* Superiority of granisetron to dexamethasone plus prochlorperazine in the prevention of chemotherapy-induced emesis. *J Natl Cancer Inst* 1991; **83**: 1169–73.
8. Bonneterre J, Hecquet B on behalf of the French Northern Oncology Group. Granisetron (IV) compared with ondansetron (IV plus oral) in the prevention of nausea and vomiting induced by moderately-emetogenic chemotherapy: a cross-over study. *J Cancer* 1995; in press.
9. Jantunen IT, Muhonen TT, Kataja VV, *et al.* 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy—a randomised study. *Eur J Cancer* 1993; **29A**: 1669–72.
10. Noble A, Bremer L, Goedhals L, *et al.* on behalf of the Granisetron Study Group. A double-blind, randomised, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. *Eur J Cancer* 1994; **30A**: 1083–8.
11. Bleiberg HH, Spielmann M, Falkson G, *et al.* Antiemetic treatment with oral granisetron in patients receiving moderately emetogenic chemotherapy: a dose-ranging study. *Clin Ther* 1995; **17**: 38–51.
12. Heron JF, Goedhals L, Jordaan JP, *et al.* on behalf of the Granisetron Study Group. Oral granisetron alone and in combination with dexamethasone: A double-blind randomized comparison against high-dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis. *Ann Oncol* 1994; **5**: 579–84.
13. Marr HE, Davey PT, Boyle EA, *et al.* Further studies of the antiemetic activity of granisetron against whole body X-irradiation or cisplatin-induced emesis in the ferret. *Pharmacology* 1994; **48**: 283–92.
14. Marty M and the Granisetron Study Group. A comparative study of the use of granisetron, a selective 5-HT_3 antagonist, versus a standard anti-emetic regimen of chlorpromazine plus dexamethasone in the treatment of cytostatic-induced emesis. *Eur J Cancer* 1990; **26** (Suppl 1): S28–32.
15. Smith IE and the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving moderately emetogenic cytostatic therapy. *Eur J Cancer* 1990; **26** (Suppl 1): S19–23.
16. Riviere A on behalf of the Granisetron Study Group. Dose finding study of granisetron in patients receiving high-dose cisplatin chemotherapy. *Br J Cancer* 1994; **69**: 967–71.
17. Chevallier B on behalf of the Granisetron Study Group. The control of acute cisplatin-induced emesis—a comparative study of granisetron and a combination regimen of high-dose metoclopramide and dexamethasone. *Br J Cancer* 1993; **68**: 176–80.
18. Jantunen IT, Flander MK, Heikkinen MI, *et al.* Comparison of ondansetron with customary treatment in the prophylaxis of nausea and emesis induced by non-cisplatin containing chemotherapy. *Acta Oncologica* 1993; **32**: 413–15.
19. Bonneterre J, Chevallier B, Metz R, *et al.* A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. *J Clin Oncol* 1990; **8**: 1063–9.

(Received 12 June 1995; accepted 26 June 1995)