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Clinical report

Efficacy and safety of oral granisetron versus i.v. granisetron in patients undergoing peripheral blood progenitor cell and bone marrow transplantation

Anthony M Abang,[1,4] Marc H Takemoto,[2] Trinh Pham,[1,5] Romeo A Mandanas,[3,6] Vivek Roy,[3] George B Selby[3] and Thomas H Carter[3]

[1]University of Oklahoma Health Sciences Center, College of Pharmacy, Oklahoma City, OK 73190, USA. [2]University of Washington Medical Center, Department of Pharmacy, Seattle, WA 92195, USA. [3]University of Oklahoma Health Sciences Center, College of Medicine, Oklahoma City, OK 73190, USA. [4]Present address: Ortho Biotech Oncology, Edmond, OK 73003, USA. [5]Present address: University of Connecticut School of Pharmacy, Storrs, CT 06269, USA. [6]Present address: Cancer Care Associates of Oklahoma City and Baptist Hospital, Oklahoma City, OK 73112, USA.

This randomized, controlled, double-blind pilot study assessed the efficacy and safety of oral versus i.v. granisetron, both in combination with non-5-HT_3 antiemetics, in preventing emesis caused by high-dose chemotherapy. Fifty-one patients who underwent peripheral blood progenitor cell transplantation (PBPCT) or bone marrow transplantation (BMT) were evaluated. Efficacy was assessed by the number of emetic episodes during the worst 24 h period. A complete response (CR) was defined as no vomiting, partial response (PR) as less than three emetic episodes and failure as three or more emetic episodes. Patients who received oral granisetron experienced significantly ($p < 0.0008$) fewer emetic episodes than those who received i.v. granisetron; however, the number of emetic episodes over the worst 24 h was similar between the oral and i.v. granisetron groups (13 and 15, respectively), as were the overall response rates (CR+PR, 54.5 and 41.4%, respectively). Both dosage forms were well tolerated. Based on these findings, further comparative studies of oral granisetron are warranted in patients undergoing PBPCT or BMT. [© 2000 Lippincott Williams & Wilkins.]

Key words: Bone marrow transplantation, emesis, granisetron, high-dose chemotherapy, peripheral blood progenitor cell transplantation.

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Correspondence to AM Abang, Ortho Biotech Oncology, 1304 Charlton Road, Edmond, OK 73003, USA.
Tel: (+1) 405 330 6112; Fax: (+1) 405 330 6105;
E-mail: AAbang@obius.jnj.com

Introduction

Although several complications of bone marrow transplantation (BMT) have been studied extensively (e.g. graft-versus-host disease, hepatic veno-occlusive disease and interstitial pneumonitis), nausea and vomiting caused by the conditioning regimens have been neglected. Up to 92% of patients undergoing treatment with high-dose cyclophosphamide may develop nausea and vomiting within 24 h after the start of conditioning therapy,[1] demonstrating the importance of emetic control in the peripheral blood progenitor cell transplantation (PBPCT) and BMT populations.

The serotonin type-3 (5-HT_3) receptor antagonists are now widely used as antiemetic therapy. Ondansetron (Zofran®; GlaxoWellcome, Research Triangle Park, NC), granisetron (Kytril®; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) and dolasetron (Anzemet®; Hoechst Marion Roussel, Kansas City, MO) are the three agents currently available in the US. These agents were originally available as i.v. formulations; however, tablet formulations of all three have since been developed, providing two routes of administration.

To date, there have been no randomized, double-blind, clinical studies comparing the efficacy of oral and i.v. granisetron in patients undergoing PBPCT or BMT. This investigation was designed as a pilot study to compare the efficacy and safety of oral granisetron with i.v. granisetron in patients undergoing these procedures.

Materials and methods

This was a randomized, double-blind, pilot trial. Patients who were to undergo PBPCT, allogeneic BMT or autologous BMT were eligible for study entry. Patients had to be 16 years of age or older and scheduled to receive one of the following conditioning regimens: oral busulfan 1 mg/kg every 6 h for 16 doses/cyclophosphamide 60 mg/kg, cyclophosphamide 1.5 g/m^2/etoposide 600 mg/m^2/carmustine 150 mg/m^2 or cyclophosphamide 60 mg/kg/etoposide 600 mg/m^2/carboplatin 500 mg/m^2. Patients were ineligible if they were unable to tolerate oral therapy, experienced nausea or vomiting 24 h prior to receiving the study medications, were hypersensitive to 5-HT_3 receptor antagonists or phenothiazines, or were concurrently receiving butyrophenones, hydroxyzine, benzodiazepines, cannabinoids or metoclopramide. Administration of prochlorperazine, lorazepam and promethazine was permitted during the study.

Written informed consent was obtained from all patients before study entry. After informed consent had been obtained, patients were stratified based on the type of transplant and conditioning regimen received. Patients were then randomized by means of a computer-generated, random list to receive either oral or i.v. granisetron. Balance between the two groups was obtained through random blocks of two.

Antiemetic regimens

Patients randomized to i.v. granisetron received 1 mg of granisetron admixed in 50 ml of 0.9% sodium chloride as a 15 min infusion administered 30 min before the start of the conditioning regimen. Those randomized to oral granisetron received a 1 mg granisetron tablet 30 min prior to the initiation of chemotherapy. To maintain blinding, patients in the oral granisetron group received a 15 min placebo infusion of 50 ml of 0.9% sodium chloride, while those in the i.v. granisetron group received a placebo tablet. The placebos, which were also administered 30 min before initiation of chemotherapy, were identical in appearance to the active drug formulations. Twelve hours after the first dose of granisetron, a second dose of granisetron and placebo was administered. Patients continued to receive granisetron and placebo every 12 h until either the day of marrow or stem cell infusion (day 0), or until the patient experienced three or more emetic episodes within any 24 h period. Chemotherapy was administered over a period of 10 days. Oral granisetron or placebo tablets were readministered if emesis occurred within 10 min of a dose. The dosing schedule of i.v. granisetron used, although not approved by the Food and Drug Administration, was chosen to match the dose of oral granisetron mg per mg while keeping the dosing schedules the same for the two formulations.

All patients received i.v. or oral lorazepam 1 mg, administered with each granisetron dose as part of the antiemetic regimen. The first five patients had a very low response rate; only one of the five patients achieved a complete response (CR) and many of the patients failed therapy 3 days after the start of chemotherapy. The protocol was therefore amended so subsequent patients received around-the-clock i.v. or oral prochlorperazine 10 mg every 6 h starting 30 min prior to initiation of the conditioning regimen. Patients 40 years old and younger also received diphenhydramine 25 mg daily for prophylaxis of extrapyramidal side effects. To enhance the efficacy of the antiemetic regimen, a change in protocol mandated that the last 17 patients received i.v. or oral dexamethasone 10 mg on each day of chemotherapy, 30 min prior to chemotherapy administration.

Evaluation of response

Patients were continuously monitored for emesis from the first dose of chemotherapy until 24 h after the last dose of granisetron. Emesis was defined as any expulsion of stomach contents through the mouth and retching was defined as an unproductive attempt to vomit. An emetic episode was a single vomit or retch, or any number of continuous vomits and/or retches. Emetic episodes that occurred within 5 min of each other were considered as one continuous emetic episode. The number, time and volume (if available) of each emetic episode was recorded by an observer blinded to therapy, usually the nurse caregiver.

Effectiveness in preventing emesis was graded according to the number of emetic episodes within the worst 24 h period, i.e. the 24 h within which the highest number of emetic episodes occurred. The rating scale used to evaluate response to treatment was CR, no emetic episodes; partial response (PR), fewer than three emetic episodes; and failure, three or more emetic episodes.

Evaluation of safety

Patients were continuously monitored for adverse events attributable to the antiemetic regimens, from the start of the conditioning regimen until 24 h after completion of the last dose of granisetron.

Statistical analysis

All statistical analyses used the intent-to-treat principle. Patient demographics were analyzed for similarities using the Mann–Whitney *U*-test. Comparison of the emetic response rates and incidence of adverse events between the two treatment groups was performed with the χ^2-test. The paired *t*-test was employed to analyze the number of emetic episodes for both arms of the trial and the log-rank test was used to compare the percentage of failure-free patients in the two study arms. A p value below 0.05 was considered statistically significant.

Results

Patient characteristics

Sixty patients who had previously received chemotherapy were randomized between January 1996 and October 1997. Eight patients (five in the oral granisetron group and three in the i.v. granisetron group) had emesis prior to administration of the study medication and were excluded from analysis. A total of 35 patients received oral or i.v. granisetron without dexamethasone and 17 received oral (n=7) or i.v. (n=10) granisetron with dexamethasone. Patients who received either granisetron treatment regimen were combined and analyzed as one treatment group. The patient characteristics are listed in Table 1. One patient, initially randomized, received therapy for 9 days and then voluntarily withdrew from the investigation and was censored from the efficacy analysis.

Table 1. Patient characteristics

	Oral granisetron	Intravenous granisetron
No. of patients	27	33
Age (years)		
median	50	48.5
range	24–66	24–65
Sex		
male	10	11
female	17	22
Race		
Caucasian	23	32
other	4	1
Diagnosis		
non-Hodgkin's disease	7	8
Hodgkin's disease	4	2
breast cancer	13	15
chronic myelogenous leukemia	1	2
multiple myeloma	1	1
myelodysplasia	1	1
lymphoma (unspecified)	–	2
testicular cancer	–	1
Waldenstrom macroglobulinemia	–	1
Preparative regimen		
etoposide/carmustine/ cyclophosphamide	11	13
cyclophosphamide/carboplatin/ etoposide	13	16
busulfan/cyclophosphamide	3	4
Transplantation type		
peripheral blood progenitor cell	24	26
allogeneic bone marrow	3	6
autologous bone marrow	–	1

Efficacy

As shown in Figure 1, the total number of emetic episodes over the 10 day period of chemotherapy was significantly ($p < 0.0008$) lower for the oral granisetron treatment group (50 episodes) than for the i.v. granisetron treatment group (104 episodes). However, on day 2, when the emetic effect of chemotherapy was most pronounced, the number of emetic episodes experienced by patients in the oral granisetron and i.v. granisetron treatment groups was similar, i.e. 12 and 15 episodes, respectively.

Table 2 summarizes the results for patients in the oral granisetron and i.v. granisetron groups. CR rates in the oral granisetron and i.v. granisetron groups were 9.1% (two of 22) and 6.9% (two of 29), respectively, and PR rates were 45.5% (10 of 22) and 34.5% (10 of 29), respectively. The overall response rates (CR+PR) were 54.5% (12 of 22) for the oral granisetron group

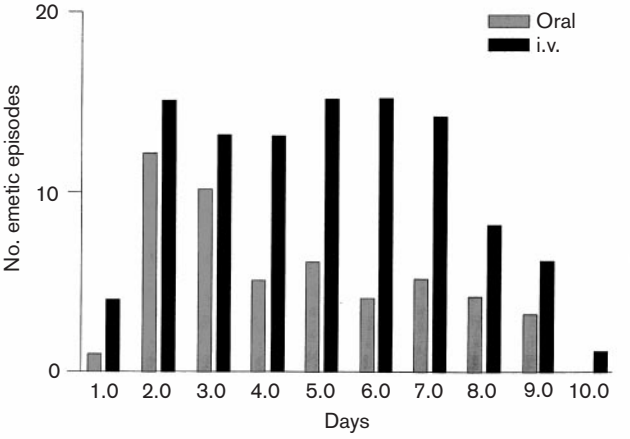

Figure 1. Comparison of the number of emetic episodes by paired *t*-test showed significantly fewer episodes for oral granisetron than for i.v. granisetron (50 versus 104 episodes, p=0.0008, two-tailed value).

and 41.4% (12 of 29) for the i.v. granisetron group. The differences between the oral and i.v. granisetron groups with respect to emetic episodes over the worst 24 h and complete, partial and overall response rates were not statistically significant.

Figure 2 presents the Kaplan–Meier survival curve of the overall efficacy (percentage of failure-free patients) for the two treatment groups and Figure 3 presents this curve for the treatment groups categorized by chemotherapy regimen. As shown in Figure 2, the percentage of failure-free patients did not differ significantly between the oral granisetron and i.v. granisetron groups (p=0.1801). Similarly, the percentage of failure-free patients did not differ significantly between the two treatment groups for patients who received cyclophosphamide, carmustine and etoposide (Figure 3A) or cyclophosphamide, carboplatin and etoposide (Figure 3B).

Response to oral and i.v. granisetron based on gender was assessed. Women tended to respond better to oral granisetron than i.v. granisetron, i.e.

Table 2. Antiemetic efficacy

	No. (%) of patients	
	Oral granisetron	Intravenous granisetron
Patients entered	22	29
male	10	9
female	12	20
Complete response[a]	2 (9.1)	2 (6.9)
male	1 (10.0)	1 (11.1)
female	1 (8.3)	1 (5.0)
Partial response[b]	10 (45.5)	10 (34.5)
male	3 (30.0)	3 (33.3)
female	7 (58.3)	7 (35.0)
Failure	10 (45.5)	17 (58.6)
male	6 (60.0)	5 (55.6)
female	4 (33.3)	12 (60.0)
Overall response[c]	12 (54.5)	12 (41.4)

[a]No emesis.
[b]Fewer than three emetic episodes.
[c]CR+PR.

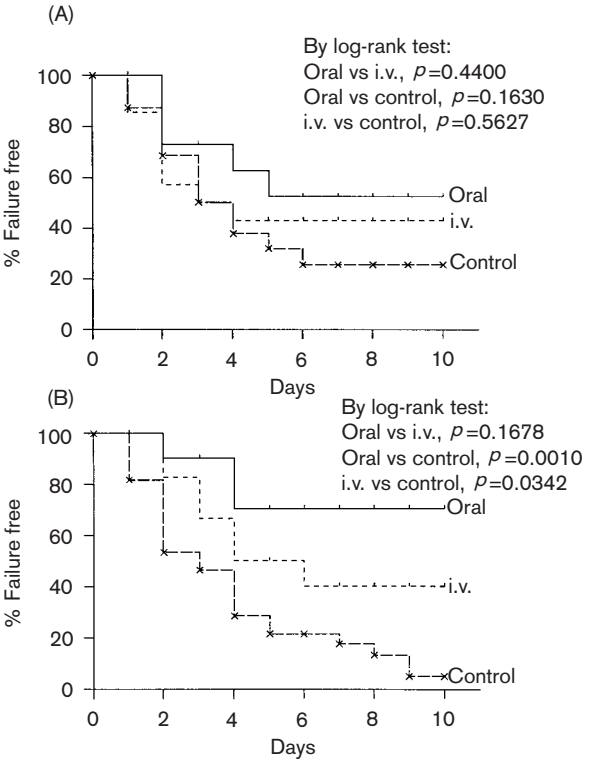

Figure 3. (A) Efficacy curve for the cyclophosphamide, carmustine and etoposide regimen. (B) Efficacy curve for the cyclophosphamide, carboplatin and etoposide regimen. 'Control' refers to historical control. See Discussion.

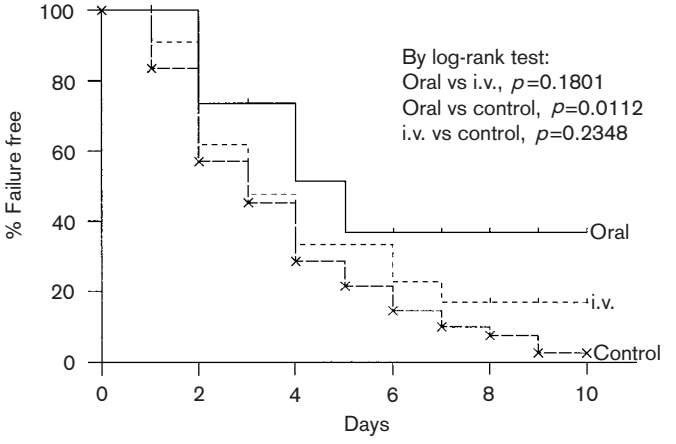

Figure 2. Overall efficacy results for oral and i.v. granisetron. 'Control' refers to historical control. See Discussion.

Table 3. Adverse events

	No. (%) of patients	
	Oral granisetron	Intravenous granisetron
Patients entered	23[a]	29
Headache	8	8
Sedation	4	5
Diarrhea	4	9
Hypertension	2	2
Hypotension	3	0
Insomnia	3	3
Jittery/EPS	3	6
Hiccups	1	6
Anxiety	2	4
Sinus congestion	2	1
Indigestion	1	3
Mucositis	1	2
Death	0	2
Confusion	0	2
Constipation	0	2

[a]Includes one patient who withdrew from the study after 9 days of therapy.

66.7% (eight of 12) versus 40.0% (eight of 20), respectively, whereas men tended to respond to oral and i.v. granisetron about equally, i.e. 40.0% (four of 10) versus 44.4% (four of nine), respectively (Table 2). It should be noted, however, that these findings were based on small numbers of patients.

Safety

Table 3 lists the adverse events seen in two or more patients in at least one treatment group. There were two deaths in the i.v. arm, neither of which was related to the study medication. One patient died subsequent to *Staphylococcus aureus* sepsis and the other died of an aspergillosis infection. Headache, diarrhea, extrapyramidal symptoms and sedation were the most commonly reported adverse events. Overall, the antiemetic agents were well tolerated and no significant difference with respect to adverse events was found between the two groups.

Discussion

In the pilot study reported here, we assessed the efficacy of the oral and i.v. formulations of granisetron in preventing emesis in patients who received high-dose chemotherapy as the conditioning regimen for PBPCT or BMT. Results were encouraging with overall response rates of 54.5 and 41.4% for patients who received oral and i.v. granisetron, respectively. These results compare to those reported in a clinical trial that investigated the efficacy of an all-oral antiemetic regimen in 36 patients who received high-dose chemotherapy prior to PBPCT.[2] The antiemetic regimen consisted of granisetron, prochlorperazine and dexamethasone; 53% of patients achieved CR (no emetic episodes within 24 h) and 75% had a combined CR and major response (zero to three emetic episodes within 24 h).

Administration of i.v. ondansetron (0.15 mg/kg/dose) 3 times a day has been the standard of practice at our institution for preventing nausea and vomiting in patients undergoing PBPCT and BMT. Ondansetron became the standard of practice based predominantly on clinical studies with patients who received standard chemotherapy regimens and not with patients undergoing conditioning regimens for BMT. Clinical trials that have compared ondansetron and granisetron have demonstrated the comparable efficacy of these agents in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy,[3–7] including comparable efficacy between oral and i.v. formulations.[8,9] We decided, therefore, to perform a retrospective chart review of patients who had previously undergone PBPCT or BMT at our institution, to determine the emetic response rates with i.v. ondansetron vis-à-vis the responses we reported for oral and i.v. granisetron. In all, 74 patients who had undergone PBPCT or BMT between January 1994 and January 1996 had records suitable for this assessment. The demographics of the 74 patients were similar to those of our study population, as were the chemotherapy regimens they had received. Antiemetic therapy for the 74 patients had consisted of ondansetron 0.15 mg/kg i.v. administered 30 min prior to cyclophosphamide, and then 4 and 8 h after the initial dose, and ondansetron 0.15 mg/kg i.v. every 8 h during busulfan and carboplatin administration. Prochlorperazine, promethazine and lorazepam were given as needed.

This group had a CR rate of 1.4%, an overall response rate of 36.5% and a failure rate of 63.5%. While these rates were less favorable than those for both granisetron groups in our pilot study, it should be noted that different antiemetic regimens had been utilized in the retrospectively reviewed group with regard to both ondansetron use and breakthrough antiemetic medications. In addition, the antiemetics had been administered on an as-needed basis, whereas in our study prochlorperazine, lorazepam and dexamethasone were administered on a regular schedule. Therefore, although the data for the present study suggest that patients undergoing high-dose chemotherapy before either PBPCT or BMT may respond better

to granisetron than to i.v. ondansetron, no definitive conclusions can be drawn regarding the overall response rates found for the granisetron and ondansetron populations. Moreover, this pilot study had a small sample size and was aimed at identifying trends that should be explored in future clinical trials rather than providing substantive information on the comparative efficacy of oral granisetron, i.v. granisetron and other available 5-HT_3 antiemetics in patients undergoing PBPC and BMT.

This study demonstrated a surprisingly low rate of CR, which may be explained by the protocol employed. First, a stringent standard for defining the CR rate (no emetic episodes) and the failure rate (three or more emetic episodes) was employed. Second, the lower response in our study may be related to the fact that patients who received total body irradiation as a conditioning regimen were excluded. It has been noted in other studies that patients who undergo conditioning regimens with total body irradiation appear to attain a higher CR rate (55–90%) than those who receive high-dose chemotherapy–conditioning regimens (0–60%).[10–12] Lastly, not all patients received dexamethasone; therefore, those patients who did not receive this agent may have had lower antiemetic efficacy, which may have influenced the overall results.

Conclusion

Analysis of the data showed that oral granisetron and i.v. granisetron had generally comparable efficacy. The safety profile for both formulations was also similar. Moreover, based on a retrospective analysis, both granisetron-based regimens were associated with a somewhat higher response rate than the i.v. ondansetron-based regimens standardly used at our institution. These findings suggest that oral granisetron may be useful for the prophylaxis of emesis due to high-dose chemotherapy in patients undergoing PBPCT or BMT, particularly if any significant savings relative to i.v. regimens can be demonstrated with respect to cost, labor or convenience of administration. Large-scale, randomized, comparative studies of oral granisetron in the setting of BMT and PBPCT are therefore warranted.

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