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An open-label dose comparison study of ondansetron for the prevention of emesis associated with chemotherapy prior to bone marrow transplantation

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Abstract Nausea and vomiting are significant side effects in bone marrow transplant (BMT) patients who receive high-dose preparative regimens. Higher than conventional ondansetron doses and continuous infusion might improve emetic control, because of the high doses and combinations of chemotherapy (CT) used in this setting. Our objective was to conduct a prospective, randomized study comparing two different administration methods of high-dose ondansetron during a BMT preparative regimen in breast cancer patients. Patients were eligible if they were nonpregnant women over 18 but under 65 years of age, undergoing highly emetogenic CT in preparation for autologous BMT. All patients received ondansetron as an intermittent (INT=24 mg i.v. q 12 h/day) or continuous intravenous infusion (CIV=8 mg i.v. loading dose followed by a continuous infusion of 2 mg/h per day). A total of 66 patients were enrolled in the study (n=34, INT; n=32, CIV). There was no statistical difference between treatment groups in the worst grade of emesis for the entire study period (P=0.49). Greater than 90% of all patients were graded as failures (≥5 emetic episodes or need for rescue antiemetics). Complete control (no vomiting episodes) and complete plus major control (1–2 emetic episodes) per day ranged from 8% to 85% and 11% to 91%, respectively. There was no significant difference between the treatment arms in: grade of emesis, episodes of vomiting and retching, nausea scores, and mean number of rescue medications administered. There were no differences in efficacy when high-dose ondansetron was given as CIV or INT for the control of nausea and vomiting in breast cancer patients undergoing high-dose CT for autologous BMT. Ondansetron alone was not adequate to provide sustained control of CT-induced nausea and vomiting over the entire 5-day study period. A combination of antiemetics targeting various mechanisms of CT-induced nausea and vomiting may be necessary to improve response rates.

Key words Ondansetron · Bone marrow transplantation · Nausea · Vomiting

Introduction

Nausea and vomiting are significant side effects in bone marrow transplant (BMT) patients who receive high-dose preparative regimens. Owing to the higher doses of chemotherapy given in preparation for BMT and to the combinations of agents administered, chemotherapy-based preparative regimens have the potential to produce more nausea and vomiting than high-dose cisplatin. In one series, nausea and vomiting was reported in 100% of BMT patients [24]. In another series of autologous BMT patients, Antman et al. observed moderate to severe nausea and vomiting despite the administration of prophylactic

antiemetics [3]. Because of the success rate of ondansetron in controlling cisplatin-induced nausea and vomiting [11], its use has been evaluated in the BMT setting.

Most studies evaluating ondansetron for BMT preparative regimens prior to the initiation of this study were small and nonrandomized [6, 8, 19, 25]. Overall response rates in these chemotherapy-based preparative regimens ranged from 9% to 82%, with complete responses varying from 9% to 67%. Dosing regimens varied from intermittent doses (0.15 mg/kg q 2 h×3 daily doses) to continuous infusions (1–3 mg/h) preceded by loading doses of 8–12 mg.

Several European studies evaluated ondansetron administered as an i.v. loading dose (8–12 mg i.v.) followed by continuous infusion of 1–4 mg/h (daily ondansetron dose ranged from 32 to 108 mg) in non-BMT patients receiving cisplatin-based chemotherapy [22]. Complete plus major response rates (0–2 emetic episodes) were similar (50–60%) over the entire dosage range. Marty et al. observed similar response rates between a single 32-mg i.v. dose and an 8-mg i.v. loading dose followed by a 1 mg/h continuous infusion of ondansetron in acute cisplatin-induced nausea and vomiting (76% vs 72% complete or major response in the single dose arm vs the continuous infusion arm) [23].

Despite the similar results observed regarding both the method of ondansetron administration (bolus vs continuous infusion) and the actual dosage administered (1 vs up to 4 mg/h), it was believed that higher than conventional ondansetron dosage regimens and, perhaps, continuous administration might be needed in the BMT setting. This is due to the higher than standard doses and the combinations of chemotherapy utilized, and also to the known variances in emetogenicity patterns. To date, no dose-limiting adverse events have been reported with ondansetron.

Although many institutions utilize ondansetron in the prevention of nausea and vomiting associated with preparative regimens prior to BMT, minimal data existed upon initiation of this study on the appropriate dose and schedule of ondansetron in this setting. Data from a large, randomized trial were needed to determine an efficacious dosing method of ondansetron in BMT patients and to assess the safety of higher doses. We wanted to evaluate a patient population receiving the same chemotherapy drugs (and hence the same emetogenic potential) on the same schedule to avoid difficulty in interpretation of results. Therefore, our objective was to conduct a prospective, randomized, non-blinded, controlled study comparing two different administration methods for high-dose ondansetron during a BMT preparative regimen in breast cancer patients.

Patients and methods

Patients were eligible for participation in this IRB-approved study if they met the following criteria: more than 18 but less than 65 years of age; non-pregnant female, with a histologically confirmed diagnosis of breast cancer, undergoing high-dose chemotherapy in preparation for autologous bone marrow transplantation; and provision of written informed consent.

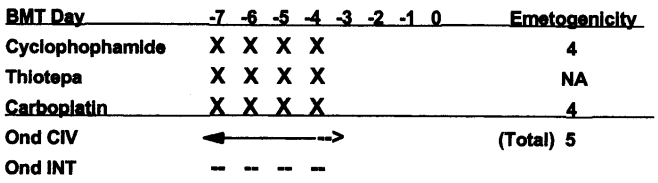

Fig. 1 Study schema. *Ond CIV* ondansetron by continuous intravenous infusion, *Ond INT* ondansetron administered intermittently. Emetogenicity according to Hesketh et al. [14]

Patients were excluded for the following reasons: a Karnofsky performance status of <60%; chronic nausea and/or vomiting or nausea and/or vomiting of other etiologies, including, but not limited to: gastric outlet obstruction, increased intracranial pressure or brain metastases; documented vomiting or retching episodes or uncontrolled nausea in the 12 h prior to the first dose of i.v. ondansetron; radiation therapy administered as part of the preparative regimen; or medications with known or potential antiemetic activity administered in the 12 h prior to the initiation of i.v. ondansetron. The restricted medications included benzodiazepines, butyrophenones, corticosteroids, cannabinoids, phenothiazines, antihistamines, tricyclic antidepressants, monoamine oxidase inhibitors, metoclopramide, trimethobenzamide, scopolamine, fluoxetine, dipravan, paroxetine and sertraline. Patients were also excluded if they required any of the restricted medications during the study period. Benzodiazepines other than lorazepam were allowed both 24 h prior to and during the study, but only when used for indications such as anxiety or to induce sleep. Premedications for transfusions, such as diphenhydramine or hydrocortisone, were not excluded.

All patients received a preparative regimen consisting of cyclophosphamide 1500 mg/m^2 i.v. q 24 h×4 doses, thio-TEPA 125 mg/m^2 i.v. q 24 h×4 doses and carboplatin 200 mg/m^2 i.v. q 24 h×4 doses (Fig. 1). All three chemotherapy agents were administered as a continuous infusion from day –7 through day –4. Recently, Hesketh et al. classified the acute emetogenicity of antineoplastic agents [14]. According their guidelines, the emetogenic potential of cyclophosphamide or carboplatin as a single agent was graded as a level 4 (60–90% emesis frequency without effective antiemetic prophylaxis; Fig. 1). Although thio-TEPA's emetogenicity is not ranked by Hesketh et al. [14], the formula he proposed to rank the emetogenicity of combination chemotherapy indicates the maximum level 5 (>90% emesis frequency without effective antiemetic prophylaxis) for this regimen.

Antiemetic therapy

Upon enrollment, patients were randomized to either an intermittent (INT) or a continuous intravenous infusion (CIV) ondansetron regimen using a 1:1 block randomization scheme. Ondansetron was administered as 24 mg i.v. q 12 h on each day of chemotherapy for the INT arm, or as an 8-mg i.v. loading dose on day 1 only, followed by a continuous infusion at 2 mg/h per day on each day of chemotherapy for the CIV arm. Ondansetron therapy was initiated 30 min before the first dose of chemotherapy for both study arms. For the INT regimen, doses were administered over 15 min in 50 ml of normal saline for injection (NS). The 8 mg loading dose was administered over 15 min in 50 ml of NS.

Clinical assessment

Patients provided a medical history and medication history and underwent a complete physical examination at the time of screening.

The history included a review of demographic information and historical status of cancer. Laboratory analysis, including blood chemistries, was conducted within 24 h before and after the study.

An episode of vomiting was defined as expulsion of any stomach contents through the mouth. An episode of retching was defined as an attempt to vomit that was unproductive of stomach contents. An emetic episode was defined as a single vomit or retch or any number of continuous vomits and/or retches. Continuous vomiting and/or retching was defined as two or more vomits and/or retches within 1 min of each other. Nausea was assessed by a numerical visual analogue scale ranging from 0 to 100 mm, with 0 mm representing no nausea and 100 mm representing the worst nausea ever experienced. Patients were asked at each 24-h interval, from day 1 of chemotherapy (day –7) through 24 h after completion of chemotherapy (day –2), to rate the degree of nausea experienced over the last 24 h. Patients, assisted by nurses when necessary, were responsible for recording the number of vomits and retches. Control of emesis was graded daily for each 24-h period as complete (zero emetic episodes); major (one to two emetic episodes); minor (three to four emetic episodes) and failure (five or more emetic episodes or the requirement of rescue therapy). The need for rescue therapy was left to the discretion of the patient and/or investigator. At the end of each 24-h period of therapy, emetic episodes were graded. If the patient required rescue therapy on 1 day, the day was graded as a failure; however, she was eligible for the next day of therapy. The number and frequency of rescue medications were documented.

Patients could be withdrawn from the study at any time at the investigator's discretion or their own request. Possible reasons for discontinuation included: unacceptable side effects associated with the study drug, discontinuation of chemotherapy because of changes in the patient's underlying disease status, and an unacceptable level of nausea and/or vomiting during the study. Patients were allowed to receive rescue medications for nausea and or vomiting if requested.

Clinical analysis

Each patient was evaluated as having been a "success" or "failure." Success was defined as complete control, major control (1–2 emetic episodes), or minor control (3–4 emetic episodes). A failure was defined as 5 or more emetic episodes or a requirement for rescue therapy. The proportion of successes and failures in each arm for each day of the study was compared. Nausea scores, number of vomits, and number of retches were also compared between study groups. The percentage of patients requiring rescue antiemetics and the number of rescue antiemetic doses administered each day were evaluated. The incidence of adverse effects were recorded.

Statistical analysis

Statistical analysis was performed using a Chi-square test or a Fisher's exact test when comparing means. A Fisher's exact test was used if half of the cells had expected counts less than 5, which makes the Chi-square test invalid. The Wilcoxon signed-rank test was used for nonparametric variables. The *t*-test was used to compare means for demographic data and number of rescue medications. The study had approximately a 70% power to detect a 30% difference in efficacy between the two arms (a 15% success rate with one group compared with a 45% success rate in the other group). Differences were considered to be statistically significant at $P \leq 0.05$.

Table 1 Demographics (*INT* intermittent administration, *CIV* continuous i.v. infusion)

	INT arm	CIV arm
No. of patients	34	32
Mean age ± SD (years)	44.1±8.3	47.9±7.3
Age range (years)	29–61	31–64
Ethnic background		
Caucasian (%)	32 (94)	30 (94)
Afro-American (%)	1 (3)	2 (6)
Syrian (%)	1 (3)	0 (0)
Disease status		
Adjuvant (%)	20 (59)	17 (53)
Metastatic (%)	14 (41)	15 (47)

Results

Sixty-six non-chemotherapy-naive patients were enrolled in the study from January 1994 through October 1995. Two patients in the INT arm withdrew because of intractable headaches. Data were analyzed for these two patients up until the time they withdrew from the study (day –5 and day –4). There were no significant differences in study results (data not shown) whether the remaining results were included or not. Thirty-four patients were randomized to INT ondansetron and 32 to CIV ondansetron. Mean age, age range, ethnicity and disease status were evenly distributed between treatment arms, as illustrated in Table 1. Means were compared with a *t*-test, and categorical variables were compared with the Chi-square test. The only significant difference (P=0.05) detected between treatment arms in Table 1 was the mean age. This difference was not felt to be clinically significant.

The worst grade of emesis was determined for each patient over the entire study period. There was no statistical difference between treatment groups in the worst grade of emesis (P=0.49, 2-tail Fisher's exact test). All 32 (100%) patients in the CIV arm and 32 (94%) patients in the INT arm had failure as their worst grade of emesis. Two (6%) patients in the INT arm had complete control of emesis throughout the study. Figure 2 illustrates the percentage of patients experiencing success (complete, major, or minor control) of emesis control per day. There was no significant difference between treatment arms in grade of emesis per day for the entire study period. The complete control

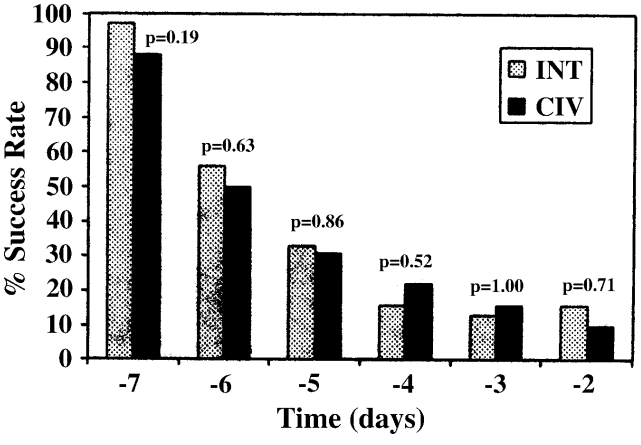

Fig. 2 Success rate. Chi-square or Fisher's exact test

Table 2 Median (range) number of vomits, number of retches, and nausea score per day

Day	INT arm			CIV arm			*P*-value [a]		
	Vomit	Retch	Nausea	Vomit	Retch	Nausea	Vomit	Retch	Nausea
–7	0 (0–1)	0 (0–4)	0 (0–82)	0 (0–2)	0 (0–7)	0 (0–20)	0.95	0.69	0.85
–6	0 (0–9)	0 (0–5)	10 (0–80)	0 (0–11)	0 (0–8)	2 (0–98)	0.90	0.34	0.32
–5	0.5 (0–30)	0 (0–12)	20 (0–100)	1 (0–10)	0 (0–8)	37 (0–100)	0.54	0.47	0.63
–4	1 (0–11)	0.5 (0–24)	30 (0–100)	1.5 (0–12)	0 (0–8)	32 (0–100)	0.96	0.39	0.96
–3	1.5 (0–6)	0 (0–12)	25 (0–99)	1 (0–8)	0 (0–5)	46 (0–100)	0.92	0.69	0.16
–2	1 (0–6)	0 (0–8)	36 (0–100)	1 (0–3)	0 (0–6)	27 (0–100)	0.17	0.10	0.66

[a] Wilcoxon rank sum test

and complete plus major control of emesis per day ranged from 8% to 85% and 11% to 91%, respectively.

Table 2 illustrates the median numbers of vomits and retches and the nausea score per day. No significant differences were detected between study arms for these three variables. Documentation of the number of retches was poor, with only 43% of 386 possible values recorded. Vomiting and nausea scores were missing in 5% and 24%, respectively.

From day –7 through day –2, the INT group received a mean (±SEM) of 11.9 (±1.4) rescue medications and the CIV group received a mean (±SEM) of 14.4 (±1.9) rescue medications (P=0.30). There was no statistical difference in the mean number of rescue medications administered between treatment groups (P=0.30). Figure 3 demonstrates the percentages of patients requiring rescue antiemetics each day. There were no significant differences noted between study arms. Additionally, no significant differences were detected in the median number of rescue antiemetic doses administered per day (range 0–4). The most common rescue antiemetics used as single agents were lorazepam and prochlorperazine. When more than one antiemetic was used per day, either lorazepam plus prochlorperazine or lorazepam plus diphenhydramine and haloperidol was prescribed. The third most common antiemetic combination utilized was lorazepam, diphenhydramine, and haloperidol.

Although antihistamines were restricted during this study, several patients received one or more antihistamine doses during the study period (most often for itching or sleep). Of the 2 patients who had an overall CR rate, 1 had received diphenhydramine and 1 had not. Other medications from the restricted list (i.e., nortriptyline and sertraline) were also inadvertently administered for treatment of nonrelated ailments. However, exclusion of these patients did not affect statistical analysis and study outcomes.

The most common adverse effects occurring during the study period are outlined in order of decreasing frequency in Table 3. Diarrhea was most common, followed by headache and elevated transaminases. The majority of the elevated transaminases were grade 0 (<2×normal) or grade 1 (2–5×normal). Other common adverse effects included constipation, musculoskeletal pain, indigestion and pruritis. There were no significant differences in the incidence of side effects between treatment groups. It was interesting to note that although the incidence of constipation was not statistically different (P=0.53) at 12% vs 31% for the INT and CIV arms, respectively, this finding may be clinically significant. Other adverse effects occurring in less than 5% of patients included: chest pain, shortness of breath, tachycardia, cough, hiccups and syncope. No extrapyramidal symptoms were reported. Owing to the complexity of drug regimens prescribed in the BMT setting, it is difficult

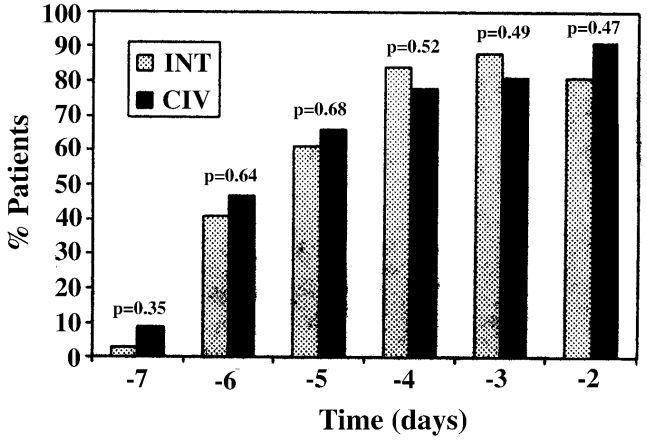

Fig. 3 Percentage of patients requiring rescue antiemetics by day. Chi-square or Fisher's exact test

Table 3 Adverse effects. Chi-square test or Fisher's exact test (P>0.05)

	INT arm	%	CIV arm	%
Diarrhea	15	(44)	15	(47)
Headache	13	(38)	15	(47)
Elevated AST	15	(44)	10	(31)
Constipation	4	(12)	10	(31)
Elevated ALT	7	(21)	3	(9)
Musculoskeletal pain	4	(12)	6	(19)
Indigestion	6	(18)	3	(9)
Pruritis	6	(18)	3	(9)
Flu symptoms (achiness)	4	(12)	2	(6)
Congestion	2	(6)	4	(13)
Insomnia	2	(6)	3	(9)
Temperature	3	(9)	2	(6)
Rash	4	(12)	0	(0)
Chills	2	(6)	1	(3)
Abdominal cramps	1	(3)	2	(6)

to attribute many of these side effects directly to ondansetron. For example, BMT preparative regimens can also be associated with diarrhea, elevated transaminases and congestion.

Discussion

During the entire study period, almost all patients (62/64) had 1 or more days rated as a failure for grade of emesis. No significant differences in efficacy or toxicity were detected between the CIV and INT ondansetron groups. Evaluation of these results by study day did not show significant differences between the two study arms. Similarly, Lazarus et al. recently compared bolus and continuous infusion granisetron (10 mcg/kg per day) in combination with dexamethasone in 43 BMT patients and found no significant differences in emetic control [20]. This study confirms our study results and suggests there are no advantages of continuous infusion $5HT_3$ antagonists over intermittent bolus doses.

Our success rates were high on the 1st day of chemotherapy (day –7), at 97% and 88% for the INT and CIV arms, respectively (Fig. 2). Interestingly, the success rate dropped to 56% and 50%, respectively, for the 2nd day of chemotherapy (day –6), and continued to decline to approximately a third of patients having success of emesis control on day –5. By the last 2 days of the study period (day –3 and –2), success rates ranged from only 10% to 16%. Barbonis et al. and Frakes et al. also identified a decline in emesis control from the 1st day of chemotherapy to the last day of chemotherapy administration [4, 10]. The inability to sustain high levels of emetic control beyond day 1 of chemotherapy suggests that nonserotonergic mechanisms associated with nausea and vomiting may contribute significantly from day 2 onward [12]. Therefore, combinations of antiemetic agents with different mechanisms of action may be necessary for improved control of emesis. Many studies have demonstrated that a serotonin antagonist in combination with dexamethasone yields better emesis control than a serotonin antagonist alone [13, 15]. Steroids were excluded in this study by other investigational protocols and the concern of increased infection risk. However, Crenier et al. compared ondansetron (8 mg i.v. q.d.-b.i.d.), granisetron (3 mg i.v. q.d.-b.i.d.), and tropisetron (5 mg i.v. q.d.) with or without dexamethasone in 34 patients receiving peripheral blood stem cell transplantation [7]. Overall, ondansetron and granisetron were more effective than tropisetron for controlling emesis, but the best control occurred when these agents were used in combination with dexamethasone. The addition of a third prophylactic antinausea medication may also be necessary in the BMT setting [9, 10].

When interpreting the success rates in our study, it is important to consider the actual number of vomits and retches that occurred per day. Failure was defined as either five or more emetic episodes per day or the need for one or more doses of rescue antiemetic therapy. The median number of vomits and retches per day was below five throughout the entire study period (Table 2). Although the percentage of patients receiving rescue antiemetics was less than 10% on the initial day of chemotherapy, this number increased over the next 2 days of chemotherapy and plateaued such that approximately 80% of patients required rescue antiemetics during the last 3 days of the study period (Fig. 3). Of those patients requiring rescue antiemetics, the median number of doses administered per day ranged from zero to 4 over the study period. Therefore, the majority of failures occurring in our study were due to the requirement for rescue antiemetics and not because patients experienced five or more emetic episodes.

When chemotherapy is given over multiple days, both an acute phase (occurring within 24 h of chemotherapy) and a delayed phase (occurring 24–72 h after chemotherapy) of nausea and vomiting may occur. For example, on day 3 (day –5) of the preparative regimen utilized for this study, patients probably experienced both “acute” nausea and vomiting from the chemotherapy agents administered on day 3 (day –5), and “delayed” nausea and vomiting from cyclophosphamide administered on days 1 and 2 (days –7 and –6). The addition of dexamethasone and/or metoclopramide may help control the delayed phase of nausea and vomiting [17]. Anticipatory nausea and vomiting, a conditioned response resulting from poor control of emesis with previous chemotherapy, may also contribute. Lorazepam may be effective in minimizing this type of nausea and vomiting [21]. Other potential mechanisms to target may include the effect of chemotherapy metabolites on the central and enteric nervous systems as well as disruption of gut motility [5].

Nausea score assessments based on the 100-mm visual analogue scale ranged from a median of 0 on the first day of chemotherapy to a maximum median of 46 on day –3 (Table 2). Beginning with the 2nd day of chemotherapy, at least 1 patient reported a daily nausea score of 98 or higher. These results are similar to the low success rates for emesis control discussed above and support the need for additional antiemetic therapy in combination with ondansetron. The mechanism of nausea is related to that for vomiting, but has different characteristics. Dexamethaone has demonstrated some efficacy for control of delayed nausea and its addition to this antiemetic regimen might have improved outcomes [16]. The missing values for number of vomits, number of retches, and nausea score emphasize the difficulty of conducting an antiemetic clinical trial. As the study progressed and patients became sicker, the compliance rate for completing study forms declined.

Overall, response rates in our study did not differ significantly from trials using more standard doses of ondansetron. Agura et al. found similar results when he compared two dose levels of ondansetron (0.1 mg/kg LD followed by 0.035 mg/kg per h vs 0.2 mg/kg LD followed by 0.07 mg/kg per h) with metoclopramide plus droperidol in 60 BMT patients [2]. Ondansetron provided better emesis control than metoclopramide plus droperidol; however,

Table 4 Summary of recent BMT studies (*CR* complete response=0 emetic episodes, *Cy* cyclophosphamide, *DEX* dexamethasone, *GRAN* granisetron, *LD* loading dose, *OND* ondansetron, *PRO* prochlorperazine, *TROP* tropisetron)

Reference	*n*	Preparative regimen	Antiemetic regimen	Response rates	
				Overall	CR
[4]	29	Carboplatin Cy or melphalan etopopside	– OND 8 mg i.v. LD then q 6 h ×3 days, then q 8 h×5 days	52–76% days 1–3 [a] 59–86% days 4–8 [a]	28–69% days 1–3 21–52% days 4–8
[10]	36	Cy etoposide or thio-TEPA carboplatin	– GRAN 2 mg p.o. q.d.+DEX 4 mg p.o. q 6 h+PRO 10 mg p.o. q 6 h×5 days	75% per day [b]	53% per day
[18]	57	Variety	– OND 24 mg i.v. q.d. or – GRAN 3 mg i.v. q.d. or – TROP 5 mg i.v. q.d. All arms – DEX 10 mg i.v. b.i.d. plus Ativan 1 mg sl t.i.d.	90.5% [c,d] 57.1% [c] 60% [c]	80.9% [d] 42.8% 20%
[1]	70	Cy-based± TBI	– GRAN 1 mg i.v. q.d. + DEX 10 mg i.v. q.d.	96% per day [a]	47% per day
Present study	66	Cy thio-TEPA carboplatin	– OND 24 mg i.v. q 12 h×8 doses or – OND 8 mg i.v. LD×1, then 2 mg/h ×96 h	13–94% per day [a] 9–88% per day [a] No significant difference between arms	9–85% per day 6–84% per day

[a] ≤2 emetic episodes
[b] ≤3 emetic episodes
[c] ≤1 vomit±nausea
[d] Superior to GRAN and TROP ($P \leq 0.03$)

on the day of worst emesis control, the low-dose ondansetron provided significantly better control than the high-dose ondansetron. This study also suggests that higher doses of $5HT_3$ receptor antagonists may not be necessary in the BMT population.

Although several other antiemetic studies in BMT patients have been reported since the initiation of this trial, it is difficult to compare them because: (1) patient populations vary with respect to history of prior chemotherapy exposure, (2) preparative regimens differ in combinations of drugs used, inclusion or exclusion of radiation therapy, and in the schedule of drug administration, (3) antiemetic combinations, dosages and duration of administration are not consistent, and (4) definitions of outcomes are not standardized. Table 4 outlines several of these trials. Overall, response rates were similar to or within the range of our study. However, overall control of emesis had a wider range in our study than seen in other studies. This may have been due to the limitation of excluding dexamethasone as a component of the antiemetic regimen. The effect of gender should also be considered. The incidence and severity of nausea and vomiting is higher in women [12], so that the results of this study performed in breast cancer patients should be evaluated with caution when they are compared with those of studies in other BMT populations.

Conclusions

There were no differences between ondansetron given as a continuous infusion (8 mg LD i.v., then 2 mg/h i.v.) or intermittent bolus dosing (24 mg i.v. b.i.d.) for the control of nausea and vomiting in breast cancer patients undergoing autologous BMT. Ondansetron as a single agent was not adequate to sustain the control seen on day 1 of chemotherapy-induced nausea and vomiting in this population. A combination of antiemetics targeting various mechanisms of chemotherapy-induced nausea and vomiting may be necessary to improve response rates. Additional study of various combinations of antiemetics in BMT recipients is needed to help determine the most efficacious regimen in these patients.

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References

1. Abbott B, Ippoliti C, Neumann J, et al (1996) Standard practice protocol of granisetron (Kytril) for antiemetic control in bone marrow transplant (BMT) patients receiving highly emetogenic chemotherapy with or without total body irradiation (TBI). Blood 88 [S1]:a3737:252b
2. Agura ED, Brown MC, Schaffer R, et al (1995) Antiemetic efficacy and pharmacokinetics of intravenous ondansetron infusion during chemotherapy conditioning for bone marrow transplant. Bone Marrow Transplant 16:213–222
3. Antman K, Eder JP, Elias A, et al (1987) High-dose combination alkylating agent preparative regimen with autologous bone marrow support: The Dana-Farber Cancer Institute/Beth Israel Hospital experience. Cancer Treat Rep 71:119–125

4. Barbounis V, Koumakis G, Vassilomanolakis M, et al (1995) A phase II study of ondansetron as antiemetic prophylaxis in patients receiving high-dose polychemotherapy and stem cell transplantation. Support Care Cancer 3:301–306
5. Beck TM (1995) The pattern of emesis following high-dose cyclophosphamide and the anti-emetic efficacy of ondansetron. Anticancer Drugs 6:237–242
6. Bosi A, Guidi S, Messori A, et al (1993) Ondansetron versus chlorpromazine for preventing emesis in bone marrow transplant recipients: a double-blind randomized study. J Chemother 5:191–196
7. Crenier L, Lemoine F, Bastin G, et al (1996) A comparative study of the efficacy of the different 5-HT_3 antagonists to control acute emesis in blood stem cells transplantation (abstract). Support Care Cancer 4:253 (abstr 116)
8. Croockewit S (1990)The efficacy of ondansetron in emesis induced by total body irradiation. Proceedings of a Glaxo sponsored symposium at the European Society of Medical Oncology Meeting in Copenhagen, 2 December pp 15–17
9. Fox SM, Einhorn LH, Cox E, et al (1993) Ondansetron versus ondansetron, dexamethasone, and chlorpromazine in the prevention of nausea and vomiting associated with multiple-day cisplatin chemotherapy. J Clin Oncol 11:2391–2395
10. Frakes LA, Brehm TL, Kosty MP, et al (1997) An all oral antiemetic regimen for patients undergoing high-dose chemotherapy with peripheral blood stem cell transplant. Bone Marrow Transplant 20:473–478
11. Glaxo Wellcome (1996) Product information for Zofran® injection. Glaxo Wellcome
12. Grunberg SM, Hesketh PJ (1993)Control of chemotherapy-induced emesis. N Engl J Med 329:1790–1796
13. Hesketh PJ, Harvey WH, Harker WG, et al (1994) A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 12:596–600
14. Hesketh PJ, Kris MG, Grunberg et al (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15:103–109
15. Italian Group for Antiemetic Research (1995) Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. N Engl J Med 332:1–5
16. Jones AL, Hill AS, Soukop M, et al (1991) Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet 338:483–487
17. Kris MG, Gralla RJ, Tyson LB, et al (1989) Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 7:108–114
18. Lacerda JF, Carmo JA, Pereira ME, et al (1996) A randomized trial of ondansetron (OND), granisetron (GRA) and tropisetron (TRO) in the prophylaxis of acute nausea and vomiting in bone marrow transplantation (BMT). Blood 88 [S1]:a1649:415a
19. Lazarus HM, Bryson JC, Lemon E, et al (1990) Antiemetic efficacy and pharmacokinetic analyses of the serotonin antagonist ondansetron (GR38032F) during multiple-day chemotherapy with cisplatin prior to autologous bone marrow transplantation. J Natl Cancer Inst 82:1776–1778
20. Lazarus HM, Creger RJ, Blumer JL, et al (1996) Randomized double-blind evaluation of bolus-dose vs continuous infusion granisetron to prevent vomiting in patients undergoing autotransplant. ISEH
21. Malik IA, Khan WA, Qazilbash M, et al (1995) Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin. Am J Clin Oncol 18:170–175
22. Marty M (1989) Ondansetron in the prophylaxis of acute cisplatin-induced nausea and vomiting. Eur J Cancer Clin Oncol 25 [Suppl 1]:S41–45
23. Marty M, d'Allens H (1990) A single daily dose (SD) of ondansetron (OND) is as effective as a continuous infusion (CI) in the prevention of cisplatin (DDP)-induced nausea (N) and vomiting (V). Ann Oncol 1[Suppl]:112 (abstract WP:14)
24. Peters WP, Eder JP, Henner WD, et al (1986) High-dose combination alkylating agents with autologous bone marrow support: A phase I trial. J Clin Oncol 4:646–654
25. Viner CV, Selby PJ, Zulian GB, et al (1990) Ondansetron – a new safe and effective antiemetic in patients receiving high-dose melphalan. Cancer Chemother Pharmacol 25:449–453