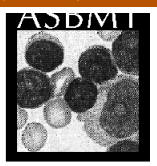

# A prospective randomized trial of the anti-emetic efficacy of ondansetron and granisetron during bone marrow transplantation

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## ABSTRACT

**To determine the comparative anti-emetic efficacy of ondansetron and granisetron in patients undergoing bone marrow transplantation, we performed a double-blind, randomized trial in pediatric and adult patients receiving transplants at the University of Minnesota. The results in 187 patients stratified by age (<18 years, n=51; ≥18 years, n=136) were analyzed. The average number of emetic episodes in the entire group from day –7 to 2 was 0.86/day for patients receiving ondansetron and 0.73/day for those receiving granisetron ($p = 0.32$). No differences were noted between the two drugs in total days of complete or major control of emesis or in the number of requests for additional drugs to alleviate symptoms of nausea. The use of total-body irradiation–containing conditioning regimens was associated with a decreased number of emetic episodes compared with regimens of chemotherapy alone. Perceived nausea was evaluated using a nausea scoring system, and no differences were apparent between the granisetron and ondansetron groups; however, reported nausea was significantly higher in females ($p < 0.01$) and in the adult population ($p = 0.05$). We conclude that both ondansetron and granisetron provide good control of nausea and vomiting experienced with conditioning regimens for bone marrow transplantation. The relative cost of the drugs within an institution must be considered in developing standard anti-emetic regimens for bone marrow transplantation.**

## KEY WORDS

Anti-emetic • Granisetron • Nausea • Ondansetron • Vomiting

## INTRODUCTION

Nausea and vomiting are major concerns of patients being treated with high-dose chemotherapy [1]. Serotonin (5-HT-3) antagonists have proven effective in providing control of nausea and vomiting, likely due to their effects on the interaction of serotonin produced by the enterochromaffin cells with receptors in the vomiting center [2]. Comparative studies have tested the most commonly used serotonin antagonists, granisetron and ondansetron, in the setting of highly emetic chemotherapy regimens and have shown them to have comparable effectiveness [2–8]. In addition, both ondansetron and granisetron have been shown to be effective during bone marrow transplantation (BMT) [9–15]. However, no trials have tested these agents in a double-blinded, randomized fashion to determine their relative efficacy in controlling emesis during the preparatory regimens associated with BMT. In addition, relatively few data are available within a single study regarding the response of children and adults to anti-emetic therapy.

This study was undertaken to determine the ability of ondansetron and granisetron to control emetic episodes and nausea during the conditioning regimen of transplantation. In addition, we sought to identify groups that may be at high risk for poorly controlled emesis and nausea. Patients receiving any of the standard conditioning regimens at the University of Minnesota were eligible, and the groups were stratified to adult and pediatric populations.

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Table 1. *Patient-related information*

| | Granisetron | Ondansetron | *p* |
|---|---|---|---|
| Number in analysis | 90 | 97 | |
| Age | | | NS |
| <18 y | 23 (26%) | 28 (29%) | |
| ≥18 y | 67 (74%) | 69 (71%) | |
| Median (range) | 41 (3–62) | 36 (2–62) | |
| Weight in kg (range) | 73 (11–132) | 71 (11–126) | |
| Recipient sex | | | NS |
| Female | 36 (40%) | 44 (45%) | |
| Male | 54 (60%) | 53 (55%) | |
| Type of transplant | | | NS |
| Autologous | 34 (38%) | 34 (35%) | |
| Allogeneic | 24 (27%) | 27 (28%) | |
| Unrelated | 32 (35%) | 36 (37%) | |
| Diagnosis | | | NS |
| Nonmalignancy | 16 (18%) | 15 (15%) | |
| Aplastic anemia | 9 (10%) | 4 (4%) | |
| Immune deficiency | 2 (2%) | 1 (1%) | |
| Metabolic disorder | 5 (6%) | 10 (10%) | |
| Malignancy | 74 (82%) | 82 (85%) | |
| Acute lymphocytic leukemia | 1 (1%) | 5 (5%) | |
| AML/MDS | 17 (19%) | 24 (25%) | |
| Chronic myeloid leukemia | 26 (29%) | 23 (24%) | |
| Lymphoma | 10 (11%) | 10 (26%) | |
| Breast cancer | 7 (8%) | 5 (26%) | |
| Other malignancy | 13 (14%) | 15 (26%) | |
| Conditioning regimen | | | NS |
| Chemotherapy and radiation | 66 (73%) | 78 (80%) | |
| Chemotherapy alone | 24 (27%) | 19 (20%) | |

*AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; NS, not significant.*

Data were collected regarding objective (episodes of emesis, overall control of vomiting) and subjective (reported nausea scores, requests for additional anti-emetic medications) criteria related to drug effectiveness. All patients in the study received either granisetron or ondansetron as well as dexamethasone, as it has been shown that dexamethasone may enhance the efficacy of serotonin antagonists [16,17].

## PATIENTS AND METHODS

### Patients

Eligible patients included individuals 2–65 years of age not currently being treated with anti-emetic medications and not having a history of recent emetic episodes preceding conditioning therapy; an exception was made for patients with nausea or vomiting due to recent anesthesia. A total of 193 patients undergoing hematopoietic cell transplantation were randomized; of those, four withdrew within 48 hours of randomization and two had inadequate data for analysis. Data on the remaining 187 patients are reported. In addition to the randomization between granisetron and ondansetron, a stratification was performed based on age (2–17 and ≥18 years of age). Patient characteristics are provided in Table 1. There were no significant differences between patients randomized to receive ondansetron or granisetron based on age, sex, diagnosis, conditioning regimen, or type of transplant (autologous, allogeneic, unrelated). Age at transplantation ranged from 2 to 62 years of age, with 51 patients (27%) <18 years old. Of patients receiving transplants, 144 (77%) received a preparatory regimen including total-body irradiation (TBI); the distribution was similar in the pediatric and adult populations (78% and 76%, respectively). Very few adult patients (five of 136, 4%) were transplanted for nonmalignant conditions, including severe aplastic anemia (SAA) and metabolic disorders. In contrast, the proportion of children transplanted for nonmalignant conditions was notably higher (26 of 51, 51%), and included patients with SAA, immune deficiencies, and metabolic disorders. While the overall distribution of autologous, related, and unrelated donor transplants was similar (36%, 27%, and 36%, respectively), a higher proportion of pediatric patients received unrelated donor transplants (35 of 51, 68%) compared with adult patients (33 of 136, 24%). In contrast, the proportion of pediatric patients who received autologous marrow (eight of 51, 16%) was lower than that of adults (60 of 136, 44%). Eight pediatric patients received marrow from a related donor (16%); 43 adult patients (32%) had a related donor.

### Study design

The objective of these investigations was to compare the relative efficacy of granisetron and ondansetron in controlling nausea and vomiting associated with BMT. The study was designed as a double-blind, randomized trial in which patients received either granisetron or ondansetron 30 minutes before the initiation of the ablative regimen; administration continued through day 0. In the ondansetron arm, patients received an initial loading dose before the start of the first dose of chemotherapy or TBI, followed by a continuous infusion. Infusions of ondansetron were administered on the basis of previous experience at our institution, ease of administration (a single infusion was prepared daily as opposed to every 4- or 6-hour dosing), and previous reports of efficacy [9,10]. An 8-mg load was administered to patients ≥18 years old followed by a 0.015 mg/kg/h drip rounded to the nearest 0.5 mg/h, amounting to ~24 mg/day for a 70-kg individual. Participants <18 years old received a 0.15 mg/kg load along with a 0.03 mg/kg/h drip rounded to the nearest 0.1 mg. A placebo consisting of an intermittent dose of 5% dextrose was administered every 12 hours. In the granisetron arm, a single intravenous dose of the drug was given before the start of chemotherapy or TBI followed by intermittent intravenous dosing of granisetron every 12 hours. Patients ≥18 years old received 7.5 μg/kg/dose (~0.5 mg for a 70-kg patient) every 12 hours; those <18 years old received 10 μg/kg/dose every 12 hours. Patients on this arm received a placebo consisting of a continuous infusion of 5% dextrose. All patients received dexamethasone, 10 mg/m$^2$/day intravenously for patients <18 years old (maximum 10 mg) and 10 mg/day intravenously for patients ≥18 years old. For "breakthrough" nausea/vomiting, additional medications were available on request. Patients ≥18 years old received lorazepam 0.5 mg or prochlorperazine 10 mg intravenously every 4–6 hours as needed. Patients <18 years old received lorazepam 0.05 mg/kg intravenously every 4–6 hours as requested or promethazine 0.25–1.0 mg/kg every 4–6 hours. Other anti-emetic support was considered as needed.

Table 2. *Nausea and vomiting: effects of ondansetron and granisetron*

| | Mean episodes of emesis/d (95% CI) | | | Mean nausea score/d (95% CI) | | |
|---|---|---|---|---|---|---|
| | Ondansetron | Granisetron | *p* | Ondansetron | Granisetron | *p* |
| All patients | 0.86 (0.67–1.05) | 0.73 (0.55–1.91) | 0.32 | 1.29 (1.13–1.45) | 1.17 (1.00–1.34) | 0.32 |
| Age <18 y | 0.87 (0.63–1.11) | 0.54 (0.27–0.81) | 0.08 | 1.14 (0.90–1.38) | 0.82 (0.55–1.09) | 0.09 |
| Age ≥18 y | 0.86 (0.63–1.09) | 0.80 (0.57–1.03) | 0.71 | 1.36 (1.15–1.56) | 1.29 (1.09–1.49) | 0.65 |

### Study parameters

To obtain objective information regarding the control of emesis, the frequency of emetic episodes was evaluated from the first day of the preparative regimen through day 2. An emetic episode was defined as expulsion of stomach contents separated by 1 minute from a previous episode; if repeated vomiting occurred with <1 minute of separation, it was considered a single episode. Retching was defined as a nonproductive emptying of stomach contents. A series of retches lasting <5 minutes was considered one emetic episode. The nursing staff recorded the number of emetic episodes as well as requests for additional anti-emetic therapy. To obtain information regarding the perception of nausea experienced by the patient, a visual analog scale containing smiling or frowning faces was used for both pediatric and adult patients to determine the severity of nausea (a 5-point scale where 0 = no nausea and 5 = worst nausea ever experienced). Visual analog scales have been used in studies with pediatric oncology patients as young as 2 years of age [18,19]. Patients were asked to report their degree of nausea on this scale daily at noon from the beginning of their ablative regimen through day 0. Control over emesis was determined based on the following determinations: complete control was defined as no emetic episodes and major control was defined as one to two emetic episodes in 24 hours. Minor control constituted more than two (three to five) emetic episodes in 24 hours, and more than five emetic episodes in 24 hours or the administration of more than two doses of rescue drugs per day defined complete failure.

### Statistical considerations

To compare the number of daily emetic episodes and nausea scores over time between the randomized anti-emetic treatments granisetron and ondansetron, we used a general linear mixed model in a repeated-measures regression analysis (SAS, PROC MIXED). To assess potentially important confounders, the following factors were also included in our models: age, sex, diagnosis (malignancy vs. no malignancy), conditioning regimen (TBI vs. no TBI), type of transplant (autologous vs. related vs. unrelated) and transplant number. Interactions between treatment groups and other predictors were also investigated.

The Mantel-Haenszel $\chi^2$ test was used for statistical comparisons of the percentage of patient days in emetic control. For daily scores, a general Wilcoxon test was performed for continuous variables, and a $\chi^2$ test was used for categorical endpoints [20].

## RESULTS

### Emetic episodes

We analyzed the number of emetic episodes as least-square means during the ablative regimen through day 2. In the entire population, the effect of the administration of granisetron vs. ondansetron was not significantly different in the control of emetic episodes. In addition, no significant differences in efficacy of granisetron or ondansetron on the control of emesis were observed in the analysis of the pediatric and adult groups individually (Table 2). In multiple regression analysis, no differences were observed between the drugs based on age, sex, diagnosis (malignancy or no malignancy), or type of transplant. Patients receiving conditioning regimens including TBI had significantly less emesis ($p = 0.04$) than individuals receiving chemotherapy alone (Table 3). Data were evaluated only in patients undergoing their first transplant (the majority of the patients receiving a

Table 3. *Risk groups for nausea and vomiting*

| | n | Mean episodes of emesis/d (95% CI) | *p* | Mean nausea score/d (95% CI) | *p* |
|---|---|---|---|---|---|
| Sex | | | 0.08 | | <0.01 |
| Female | 80 | 0.97 (0.63–1.30) | | 1.63 (1.34–1.92) | |
| Male | 107 | 0.69 (0.52–0.86) | | 1.31 (1.06–1.26) | |
| Age | | | 0.71 | | 0.05 |
| <18 y | 51 | 0.82 (0.47–1.17) | | 1.33 (1.03–1.63) | |
| ≥18 y | 136 | 0.88 (0.59–1.16) | | 1.60 (1.36–1.84) | |
| Conditioning | | | 0.04 | | 0.2 |
| Containing TBI | 141 | 0.73 (0.56–0.89) | | 1.14 (1.00–1.29) | |
| Chemotherapy alone | 35 | 1.06 (0.77–1.34) | | 1.33 (1.07–1.60) | |

*Multiple regression analysis of emetic episodes and reported nausea in groups undergoing the ablative regimen of bone marrow transplantation. For determinations of the effects of a conditioning regimen containing either TBI or chemotherapy alone, only patients undergoing their first transplant were considered in the analysis.*

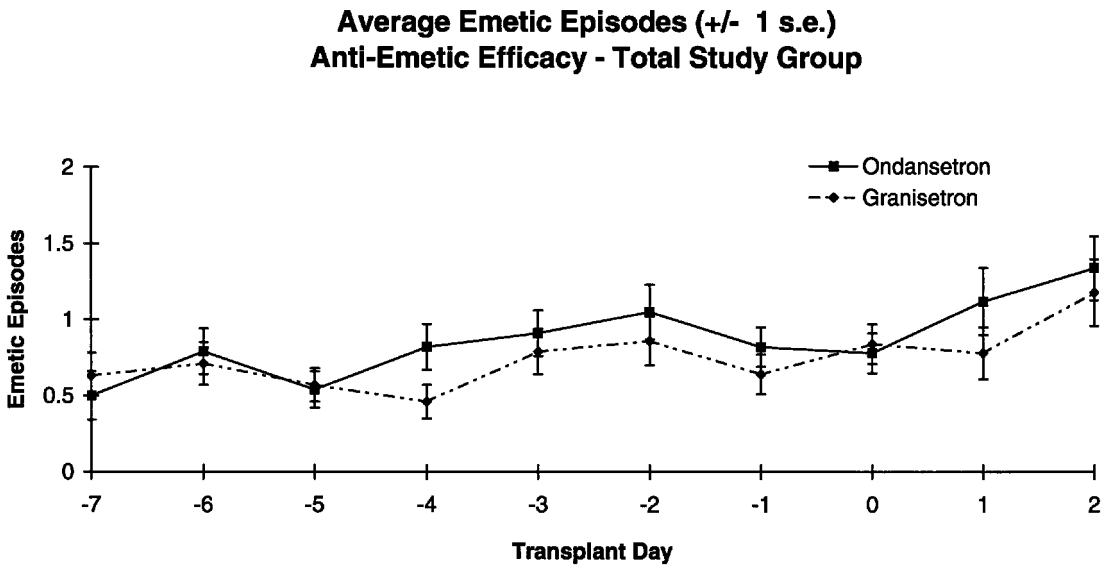


Figure 1. Daily mean emetic episodes

*Mean number of emetic episodes experienced by all patients daily during the preparatory regimen associated with transplantation from day –7 to day 2.*

second transplant received a chemotherapy-based regimen, which could represent a confounding variable). It should be recognized that patients undergoing transplantation with TBI may have different diagnoses than those undergoing transplants with chemotherapy alone and may have had varying exposures to chemotherapeutic agents before their transplant experience, which could influence emesis during their BMT. We observed that the number of emetic episodes was relatively constant during the entire preparative regimen (Fig. 1). However, there appeared to be an increase in the number of episodes after day 0, primarily in the pediatric population, when the anti-emetic therapy was stopped. This phenomenon was less evident in the adult population.

### Nausea scor es

In the entire group, we observed no significant differences between the granisetron and ondansetron arms in nausea experienced by patients. In addition, no significant differences in the reported nausea was observed when the adult and pediatric populations were evaluated individually (Table 2). In multivariate analysis comparisons, female patients experienced more nausea than male patients ($p < 0.01$). In addition, less nausea was reported by the pediatric group in comparison to the adult group ($p = 0.05$). No differences were apparent in the nausea experienced with conditioning regimens with or without TBI. The severity of nausea did not appear to increase over time during the preparative regimens (Fig. 2), but data were not collected on perceived nausea later than day 0, so correlation with the increased number of emetic episodes could not be assessed.

### Degr ee of emesis control and administration of rescue medications

Assessments were made of the number of days of complete, major, and minor control and complete failure for both drugs. The data were evaluated as both the proportion of days with complete control as well as the number of days with complete and major control; no differences were observed in either case (Fig. 3). Information regarding the number of requests for additional anti-emetic medications was analyzed based on the number of days in which no requests were generated vs. days when there were any requests for additional medications, as well as by two or more drugs requested daily vs. less than two drugs. No differences were observed for the two drug regimens tested (Fig. 4).

### Safety

Both drugs were well tolerated. In one case (granisetron arm), the drug was discontinued because of headaches. Similar numbers of patients in each group reported difficulties with headache (13 patients in each group), diarrhea (granisetron, six; ondansetron, two), dizziness (granisetron, four; ondansetron, two), and joint pain (granisetron, five; ondansetron, one). Less commonly reported effects included anxiety, hiccoughs, heartburn, and burning/flushing of the skin. No differences in survival were determined at 30 and 100 days posttransplant.

## DISCUSSION

In this single-institution trial, we compared the capacity of granisetron and ondansetron to control nausea and vomiting for patients undergoing BMT. Although serotonin antagonists have been shown to be well tolerated and more effective than other agents in the conditioning phase of transplantation [9,10,12,13,15], no randomized, blinded comparison has been performed in this setting between the two most commonly used drugs, ondansetron and granisetron. For all measures of this important complication of transplantation, no significant differences were observed between the drug regimens tested in the overall transplant population. There

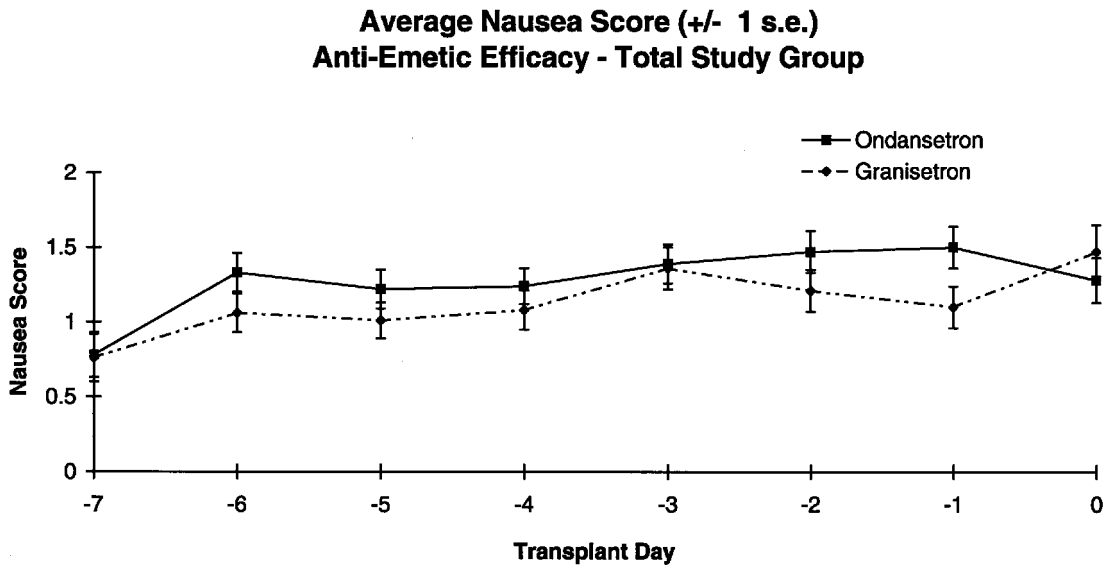


Figure 2. Daily mean nausea scores

*Average nausea score in the entire population of patients as reported daily during the preparatory regimen from day –7 to day 0.*

was a trend toward greater control of both emesis and nausea in the pediatric patients using granisetron ($p = 0.08$ and 0.09) that did not achieve significance. Because granisetron is less costly in our institution, it is used preferentially in our BMT patients. Additional savings may be achieved in the use of oral agents, since there is evidence in patients receiving chemotherapy and in patients undergoing BMT that adequate control may be maintained without the requirement for intravenous administration [11,21–23].

We observed very good overall control of emesis, with complete control achieved in >60% of patient days for both drugs, and major control (one to two episodes of emesis/day) apparent in an additional 27% of patient days. It is unclear how much the use of dexamethasone contributed to this control, since we have not previously tested the efficacy of the serotonin antagonists alone. Others have observed a benefit from the inclusion of dexamethasone with these agents, however [17,24]. Others have reported

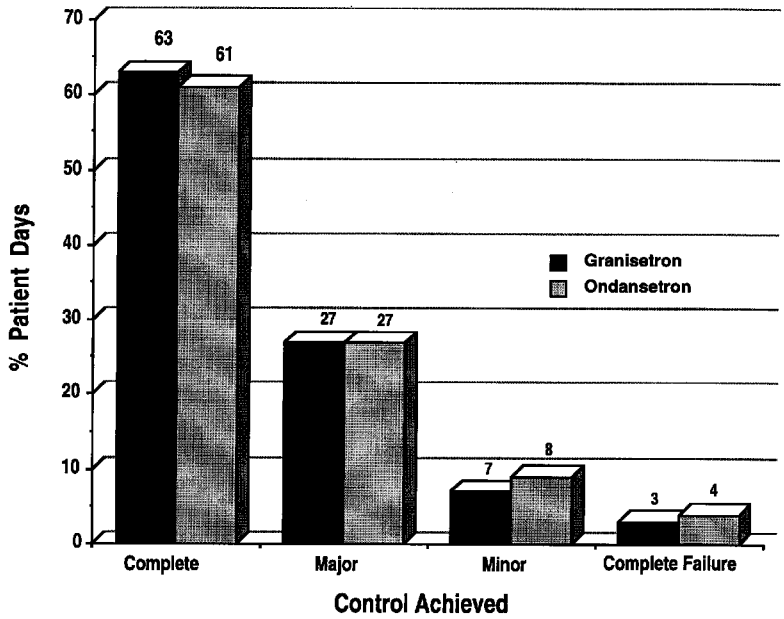


Figure 3. Control of emesis

*Proportion of days in which emesis control is complete, major, minor, or uncontrolled in patients receiving granisetron and ondansetron. Comparison of days achieving complete control, $p = 0.68$; comparison of days achieving complete and major control, $p = 0.68$.*

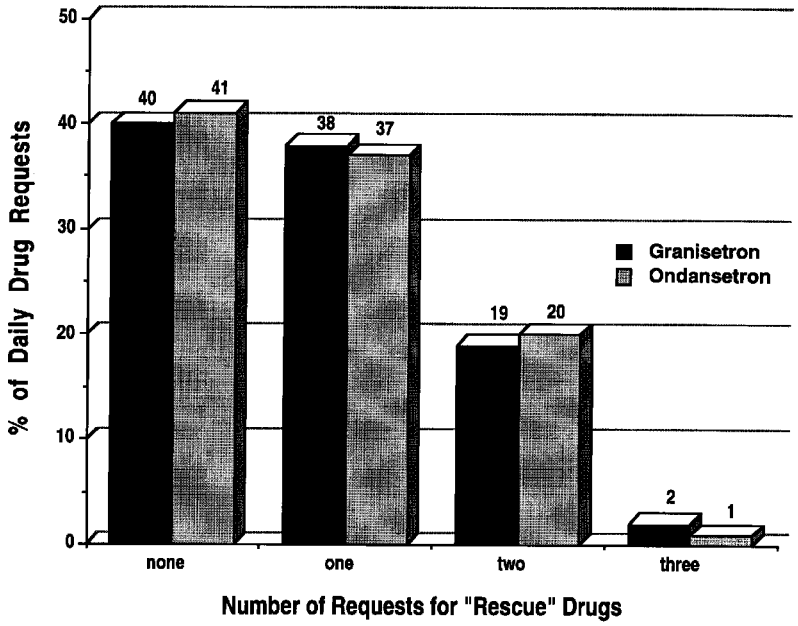


Figure 4. Requests for additional anti-emetic medications

*Number of days in each category for patients receiving granisetron and ondansetron. Comparison of days of any additional drugs to none, $p > 0.80$; comparison of days of >2 requested drugs to <2 drugs, $p > 0.80$.*

findings similar to ours in patients undergoing BMT, including a study in which patients were randomized to receive dexamethasone and 1 mg granisetron once (38% complete, 41% major control) or twice (45% complete, 43% major control) a day [25]. No data on mean number of emetic episodes were provided. Gibbs reported a nonblinded but randomized study in which patients undergoing 3–4 days of TBI were randomized to receive oral ondansetron (8 mg twice a day throughout TBI) or a single dose (3 mg) of intravenous granisetron at the beginning of therapy only. In that study, the control achieved with ondansetron or granisetron was comparable in the first 24 hours, but a single dose of granisetron was found to be less effective by the end of therapy [26]. Both of our tested anti-emetic regimens compare favorably with observations reported from other transplant centers.

We used a continuous infusion of ondansetron in our study based on our previous experience and reports of effectiveness observed by others using an infusion of ondansetron at a comparable dose (0.035 µg/kg) [9]. Because the drug requires frequent dosing, and because it can be prepared as a single 24-hour infusion, the cost of administering it as a single infusion is comparable despite the use of a continuous infusion pump. Patients generally have a double-lumen right atrial catheter, and during the preparative regimen one lumen is dedicated to chemotherapeutic agents and the other to the ondansetron, thereby avoiding potential incompatibilities. Because granisetron has a longer half-life, little information is available regarding its use as a continuous infusion; however, it is possible that it may also prove effective.

While the majority of studies include only adults, studies in pediatric populations undergoing BMT have shown that ondansetron (0.15 mg/kg every 4–6 hours) achieved rates of complete (41%) and major (30%) responses similar to those in adults. Patients in this study had a mean of two episodes of emesis daily [14]. At the Dana Farber Cancer Center, complete or major control was achieved in 67% of pediatric patients undergoing transplantation when a loading dose of 0.15 mg/kg ondansetron was administered followed by a infusion of 0.019 mg/kg/h [15]. Our results suggesting greater control of emesis may be due to variations in the dose of ondansetron (continuous infusion of 0.03 mg/kg/h) or the use of dexamethasone [16,27]. While there is information regarding the use of granisetron in a pediatric population to prevent nausea associated with chemotherapy [28,29], we are unaware of other studies reporting its use in children undergoing transplantation regimens.

In multiple regression analysis, patients receiving a preparative regimen other than TBI experienced a significantly increased risk of emesis ($p = 0.04$). This analysis was performed only in individuals receiving their first BMT, as undergoing a second or third transplant may be associated with additional toxicity that could be reflected in the degree of emesis. In addition, patients undergoing a subsequent transplant are more likely to receive a preparative regimen consisting of chemotherapy alone and not TBI. Additionally, it should be noted that patients transplanted with TBI-containing regimens may have had different diagnoses than those receiving chemotherapy alone, and therefore may have had different therapy before transplantation. This difference could also be important in the number of emetic episodes observed during BMT. The association of TBI-containing regimens with comparatively less nausea and vomiting has been observed [14,15]. In our study, however, there was no significant difference in reported nausea between conditioning regimens.

Evaluation of nausea scores revealed that females had more reported nausea than males ($p < 0.01$). Differences in nausea or vomiting between the sexes has been previously described [2,9,23], although we did not observe a significant difference in the number of emetic episodes between females and males. Evaluation of the effect of age on nausea and vomiting revealed that children were less likely to report severe nausea than adults ($p = 0.05$). While few prior studies have made such a comparison, these observances may be in part due to reporting differences within the younger and older pediatric patients, as children in the 5- to 9-year-old age group reported less nausea (mean nausea score 1.04; 95% confidence interval [CI] 0.77–1.31) than the 15- to 17-year-old transplant recipients (mean score 1.82; 95% CI 1.20–2.44).

Our data on the frequency of emesis suggest that there may be delayed vomiting observed over several days post-transplant, especially in the pediatric population. Documentation of delayed nausea and vomiting was not an initial focus of this study, but in early patients there was a suggestion of delayed emesis and additional information on emesis was obtained from subsequent patients; however, we did not collect data on the degree of nausea patients experienced after day 0 and so cannot correlate the vomiting observed with nausea scores. It may prove useful to monitor patients for these delayed effects. Whether serotonin inhibitors or other agents such as dexamethasone alone are the optimal therapy for delayed vomiting is unclear [2,23,30,31].

In summary, the use of granisetron or ondansetron along with dexamethasone was comparable in the control of nausea and vomiting associated with the conditioning phase of transplantation in both children and adults. Both regimens were well tolerated. Therefore, cost considerations should be an important determining factor in the choice of these agents at each institution.

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