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Prevention of Nausea and Vomiting Associated with Stem Cell Transplant: Results of a Prospective, Randomized Trial of Aprepitant Used with Highly Emetogenic Preparative Regimens

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A B S T R A C T

Uncontrolled delayed nausea and vomiting remains a problem after high-dose preparative regimens used for autologous and allogeneic hematopoietic stem cell transplants. Recently, aprepitant was approved for highly and moderately emetogenic chemotherapy, and, in particular, is effective for decreasing delayed emesis. To evaluate its safety and efficacy in the transplantation setting, we performed a randomized, placebo-controlled, phase 3 trial of aprepitant in combination with ondansetron and dexamethasone in patients treated with ablative preparative regimens. Patients were randomized to receive oral aprepitant or placebo daily with oral ondansetron and dexamethasone during and for 3 days after the completion of the preparative regimen in this prospective randomized, double-blind study. The primary objective was complete response (CR) rate, defined as no emesis with no or mild nausea. Other endpoints included number of emetic episodes, nausea severity assessed using a 100-mm visual analog scale (VAS), the need for rescue antiemetics, and transplantation outcome, including regimen-related toxicity. One hundred eighty-one patients were randomized and 179 patients were eligible for analysis. Overall, CR rates were 81.9% for the aprepitant and 65.8% for the placebo arms ($P < .001$). Percentages of patients with no emesis all days were 73.3% for aprepitant and 22.5% placebo ($P < .001$). Mean VAS scores were 16.6 mm aprepitant and 16.9 mm placebo (NS), and there were no differences in the amount of rescue antiemetics used, regimen related toxicity, engraftment, or transplantation outcome. Aprepitant in combination with dexamethasone and ondansetron significantly decreased emesis and significant nausea, whereas not increasing RRT or affecting short-term survival but had no significant impact on the use of PRN antiemetics, or overall VAS nausea scores.

INTRODUCTION

Prevention of nausea and vomiting remains a challenge for patients receiving highly emetogenic preparative regimens before stem cell transplant despite the use of 5-HT_3 antagonists [1]. The 5-HT_3 antagonists are effective in preventing acute nausea and vomiting in this patient group; however, control decreases rapidly over the days of the preparative regimen from 90% on day 1 to 10% by the end of the preparative regimen [2]. This is likely because serotonin release is not a major etiologic factor in the delayed phase of chemotherapy-induced nausea [3].

Aprepitant is a neurokinin-1 antagonist that interferes with the effects of the neuropeptide, substance P [4]. In animal studies, neurokinin-1 antagonists are effective in controlling emesis induced by emetogenic stimuli against which 5-HT_3 antagonists have little effect, including apomorphine, loperamide, copper sulfate, and motion-induced emesis [4,5]. It is Food & Drug Administration (FDA)-approved and administered for 3 days to patients receiving highly and moderately emetogenic chemotherapy, where its major impact is in preventing delayed nausea and vomiting in naively treated patients [6-10]. The etiology of nausea and vomiting in the stem cell transplant population is multifactorial and includes anticipatory effects in these typically heavily treated patients, side effects of prophylactic antibiotics and narcotic analgesics, and the high-dose preparative regimens that lead to a poor end-of-regimen control rate, making aprepitant an attractive addition to standard antiemetic regimens for these patients.

However, as transplantation preparative regimens typically take up to a week to administer, it is important to provide effective drug levels throughout the preparative regimen and 3 days beyond or significantly longer than the drug is currently used, which could have toxicity implications. When used only 3 days as approved by the FDA, aprepitant is a substrate for and moderate inhibitor of CYP3A4 and a mild inducer of CYP2C9. However, when used for more than 7 days, aprepitant may actually act as an inducer of CYP3A4 [11,12]. As both etoposide and high-dose cyclophosphamide are metabolized by CYP3A4, so aprepitant could theoretically affect the transplantation outcome as well as regimen-related toxicity (RRT) in this setting.

Therefore, we conducted a prospective, randomized, double-blind phase III trial of aprepitant for the prevention of

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nausea and vomiting associated with highly emetogenic preparative regimens before stem cell transplant (SCT), in which the aprepitant was given daily during and for 3 days after the preparative regimen finished with endpoints of both efficacy and toxicity as measured by engraftment, RRT, and progression-free survival (PFS) and overall survival (OS) [13]. As such, the trial required an investigational new drug number due to its non-FDA-approved dosing and was registered at ClinicalTrials.gov Identifier NCT00781768.

PATIENTS AND METHODS

Design

This study was a single-center, comparative, randomized, double-blind, phase III trial designed to evaluate the efficacy of oral aprepitant (Emend; Merck & Co., West Point, PA) in combination with ondansetron and dexamethasone in the prevention of acute and delayed nausea and vomiting compared to ondansetron and dexamethasone alone in patients receiving highly emetogenic preparative regimens before autologous or allogeneic SCT. The protocol was approved by the institutional review board, and written informed consent was obtained from each patient.

Patients

Eligible patients were at least 18 years of age, had malignant disease, consumed <5 alcoholic drinks per day in the past 1 year, and were scheduled to receive 1 of 5 myeloablative high-dose cyclophosphamide preparative regimens before SCT: total body irradiation (TBI)/etoposide/cyclophosphamide (Cy) [14] (TBI 1200 Gy fractionated into 8 doses on days -8, -7, -6, and -5, etoposide 60 mg/kg i.v. over 4 hours on day -4, Cy 100 mg/kg i.v. over 2 hours on day -2), busulfan (Bu)/Cy [15,16] (oral Bu 0.875 mg/kg/dose or i.v. Bu 0.8 mg/kg/dose every 6 hours × 16 doses given on days -7, -6, -5, -4 and Cy 60 mg/kg i.v. over 1 hour on days -3 and -2), etoposide, cytarabine, melphalan/VP/Cy [17] (carmustine 15 mg/kg i.v. over 2 hours on day -6, etoposide 60 mg/kg i.v. over 4 hours on day -4, Cy 100 mg/kg i.v. over 2 hours on day -2), and TBI/Cy [18] (TBI = 1200 cGy fractionated into 8 doses on days -7, -6, -5, and -4, and Cy 60 mg/kg i.v. over 1 hour on days -3 and -2). Patients were required to have an estimated creatinine clearance of at least 50 mL/minute and normal liver function, defined as a total bilirubin less than 1.5 × upper limit of normal and an aspartate aminotransferase <2 × upper limit of normal.

Procedures

Patients who met the eligibility criteria were stratified by gender [13] and randomized to 1 of 2 treatments: dexamethasone 7.5 mg i.v. once daily and ondansetron 8 mg orally every 8 hours on each day of the preparative regimen plus 1 additional day combined with aprepitant; 125 mg orally on the first day of their preparative regimen followed by 80 mg daily on each remaining day of the preparative regimen plus 3 additional days; or dexamethasone 10 mg i.v. once daily and ondansetron 8 mg orally every 8 hours on each day of the preparative regimen plus 1 additional day plus aprepitant placebo. As noted above, the dose of blinded dexamethasone varied because of a known drug interaction between it and aprepitant. Lorazepam was used for breakthrough nausea or vomiting and was allowed as needed for anxiety, catheter insertion, and sleep. Phenytoin [1 g loading dose day 1, then 400 mg daily (days -7 to -2] was used as seizure prophylaxis in patients receiving i.v. Bu/Cy. Prochlorperazine was allowed only for repeated episodes of vomiting (defined as >4 episodes in any 12-hour period).

Assessments

Episodes of vomiting as well as any rescue antiemetics were recorded. Retching was counted as an emetic episode. For the purpose of determining risk factor balance in all arms, patients were asked to fill out a questionnaire pertaining to their history of nausea and vomiting associated with prior chemotherapy, radiation, or pregnancy as well as history of motion sickness or anticipatory nausea and vomiting. Self-grading of nausea was performed daily using a visual analog scale (VAS), a 100-mm line marked no nausea at one end (0 mm) and severe nausea at the other end (100 mm).

Evaluation of Response

The primary efficacy endpoint was to determine and compare the rate of complete response (CR; defined as no emesis with only grade 1-2 nausea: patient able to eat; reasonable intake, using National Cancer Institute Common Toxicity Criteria 3.0) during and 3 days after high-dose therapy in patients treated with aprepitant in addition to oral ondansetron and i.v. dexamethasone compared to the standard regimen of oral ondansetron and i.v. dexamethasone in the stem cell transplant setting. The secondary efficacy endpoints were to compare the degree of nausea, as measured using the VAS, and total number of antiemetic breakthrough doses administered in each arm of the study.

Overall nausea was analyzed by averaging daily VAS scores in each arm of the study. Major and minor responses and failure rates were also determined. Major response (MR) was defined as 1 episode of vomiting or if no vomiting occurred, moderate nausea (intake significantly decreased but patient can eat) with rescue antiemetics allowed. Minor response (mR) was defined as 2 to 4 episodes of vomiting regardless of nausea or rescue antiemetic use. Failure (F) was defined as >4 episodes of vomiting regardless of nausea or rescue antiemetic use. Major efficacy (ME) was defined as complete responders plus major responders. Daily responses were averaged and results are reported as composite scores.

The primary toxicity endpoint was to determine RRT and 1-year survival rate. RRT was measured by documenting engraftment and all non-myelosuppressive grade III or IV toxicity during and after the first 30 days after the completion of the last dose of aprepitant. WBC engraftment was defined as the first day the absolute neutrophil count reached 500/μL sustained for 3 consecutive days, and platelet engraftment was defined as the first of 7 days the platelet count reached 20,000/μL without transfusion.

The definition of CR allowed the use of lorazepam because its use in this patient population was universal for various indications, including anxiety and insomnia; however, an additional analysis was done to determine the percentage of patients with no emesis, less than grade 3 nausea, and no rescue (PRN) medications over the entire 8- to 10-day treatment period.

Statistical Methods

The study design was a stratified 2-sample binomial proportions controlled trial. Based on our earlier hematopoietic stem cell transplant antiemetic study [2], it was estimated that, for the control arm, the absence of emesis during the preparative regimens would be approximately 30%. By modeling based on aprepitant studies in highly emetogenic standard dose chemotherapy, we determined that a complete control rate of 50% would be expected. Based on this, the estimated sample size was 90 patients per arm, which would provide 80% power to detect a difference of 20% between the null hypothesis that both groups have a 30% delayed emesis rate and the alternative hypothesis that the no emesis rate in the experimental group is 50% with a significance level (alpha) of 0.05, using a 2-sided 2-sample *t* test based on the normal approximation to the binomial distribution.

All study variables are summarized using descriptive statistics. Independent *t* tests were used for continuous, normally distributed data to compare the 2 groups. For data that was not normally distributed, the nonparametric Pearson Chi-Square and the Mann-Whitney *U* statistics were used to determine associations between the 2 groups. All nominal data using the 1-year OS and 1-year PFS were calculated using the Kaplan-Meier method, and the difference in survival rate was determined by the log-rank test.

Statistical analyses were performed using SPSS for Windows (SPSS, Inc., Chicago, IL) with significance determined at a 2-sided level of <.05.

RESULTS

Patients

A total of 264 eligible patients were seen during the registration period between September 2004 and July 2008 (Consort Diagram; Table 1). Of these, 181 were randomized into the study. The majority of those not enrolling declined, citing concerns of increased RRT or the potentially diminished efficacy of the transplantation. Two randomized patients never proceeded to transplantation and did not receive the study drug. They are not included in the analysis. Ten patients withdrew consent during the trial (6 in the aprepitant arm and 4 in the placebo arm). Four patients withdrew due to side effects: 1 patient in the placebo arm quit due to a panic attack; 3 patients withdrew in the aprepitant arm due to seizures with visual hallucinations, dizziness, and anxiety, respectively. The remaining 6 patients (3 in each arm) quit due to poor nausea and/or emesis control.

Treatment groups were stratified based on gender and were balanced with respect to age, weight, and history of nausea and vomiting with prior chemotherapy (Table 2). Results of the questionnaire pertaining to history of nausea and vomiting are reported in Supplementary Table S1.

All patients who received the study drug were included in the intent-to-treat analysis. Overall, 1597 of 1644 (97%) VAS