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Aprepitant for prevention of nausea and vomiting secondary to high-dose Cyclophosphamide administered to patients undergoing Autologous Peripheral Blood Stem Cells mobilization: A Phase II Trial

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Abstract

This is a phase II trial evaluating efficacy and safety of Aprepitant (AP) in combination with 5-HT₃ antagonist and adjusted dose dexamethasone in patients receiving high-dose cyclophosphamide (CY) and filgrastim for stem cell mobilization. We used Simon's optimal two-stage design constrained to fewer than 40 patients with 10% type I error and 85% statistical power. The first stage of the study required accrual of 18 response-evaluable patients. The primary endpoint was the control of vomiting without the use of any rescue anti-emetics at 24 hours after the administration of high dose CY (4gm/m²). If emesis was controlled in 9 patients, an additional cohort of 17 patients would be enrolled. The null hypothesis would be rejected if there were 20 responses among 35 patients. Forty patients were enrolled, five of whom were not evaluable for response. Eighteen evaluable patients were enrolled in the first stage. Acute emesis was controlled in 10 patients; therefore, enrollment proceeded to stage 2. An additional 17 patients were enrolled; 20/35 response-evaluable patients (57%) did not develop acute vomiting or require rescue anti-emetics, thus achieving the goal of the study. A total of 22/35 response-evaluable patients (63%) met the secondary endpoint of delayed emesis control (days 2–5). Thirty three out of 35 patients underwent successful stem cell mobilization. No grade 3 AP-related adverse events were noted. The AP regimen can effectively control acute and delayed emesis in the majority patients receiving high-dose CY.

Keywords

Aprepitant; nausea; vomiting; high-dose cyclophosphamide

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Disclosure/ Conflicts

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Introduction

Nausea and vomiting are symptomatic side effects of chemotherapy that are both physically and psychologically burdensome. Approximately 80% of patients receiving chemotherapy experience nausea and/or vomiting [1], affecting patients' quality of life and potentially leading to anticipatory nausea/ vomiting in 10–44% of patients [2]. The emetic potential of chemotherapy varies with the class of the chemotherapy agent and its dosage. Agents like cyclophosphamide (CY), doxorubicin, epirubicin, oxaliplatin, carboplatin and irinotecan are categorized as moderately emetogenic chemotherapy (MEC). American Society of Clinical Oncology (ASCO) recently updated guidelines for the use of anti-emetics with high dose chemotherapy conditioning regimens suggest to use AP in combination but also acknowledges limited supportive evidence [3]. For patients undergoing treatment with an anthracycline and CY, the recommendation is to use the three-drug regimen of a 5-HT₃ receptor antagonist, dexamethasone, and selective neurokinin-1 receptor blocker prior to chemotherapy, followed by a NK1 receptor antagonist and/or dexamethasone after chemotherapy.

Aprepitant (Emend ®) is a selective, high-affinity antagonist of human substance P/NK1 receptors, with little or no affinity for dopamine, serotonin and corticosteroid receptors [4]. Substance P acts at the NK₁ receptor in the gastrointestinal fibers and the brainstem and is considered to play a role in emesis induction when these receptors are stimulated by radiation and/or chemotherapy [5]. Aprepitant's (AP) unique mechanism of action has translated into useful clinical benefit. Several large clinical studies established that addition of AP to a 5-HT₃ receptor antagonist and dexamethasone improves prevention of chemotherapy induced nausea and vomiting (CINV) in patients receiving high and moderately emetogenic chemotherapy (HEC and MEC) [6, 7, 8 and 9]. In patients receiving cisplatin 70mg/m², a HEC agent, complete response (no emesis and no rescue therapy) was maintained from 64–59% between cycles 1–6 in AP group. In comparison the standard therapy group had significantly reduced emesis control of 49–34% between cycles 1–6 [8].

AP is increasingly used in hematopoietic stem cell transplant (HSCT) patients; however, efficacy data in HSCT patients is missing. There are no clear ASCO guidelines for the use of anti-emetics with preparative regimens given prior to HSCT. The Multinational Association of Supportive Care in Cancer (MASCC) guidelines from 2009 recognize the difficulty in evaluating patients undergoing HSCT given the multi-factorial nature of the nausea and vomiting and suggest a need for evaluating the efficacy of AP added to standard anti-emetic therapy [10]. Given the lack of consistent recommendations and strategies, HSCT programs have devised institutional guidelines for antiemetic regimens. In addition, AP has a complex metabolic pathway, being a CYP3A4 substrate, a 3A4 inhibitor and an inducer, and a 2C9 inducer, which could theoretically lead to clinically significant and unexpected drug interactions [11]. AP may have the potential to decrease activation of agents like CY and ifosfamide (which are activated by CYP3A4), thereby possibly decreasing anti-tumor effects [12], but a recent publication, demonstrated no negative effects in regards to CY pharmacokinetics and AP efficacy [13]. No empiric dose-adjustments are currently recommended for concurrent chemotherapy if patients receive AP.

Procedures for mobilization of autologous peripheral blood stem cells (PBSCs) are not standardized. Adequate yield of PBSC is feasible using high dose CY and growth factors [14], especially in myeloma patients treated with novel drugs [15]. Nausea and vomiting induced by CY-based chemotherapy has a long latency of onset (8–13 h) and continues for at least 3 days. Previous studies with high-dose CY in non-transplant settings have shown that more than 80% patients experience nausea and/or vomiting, no good data exists for patients undergoing HSCT [16]. Use of ondansetron for anti-emetic control in patients

receiving intermediate-dose CY is associated with nausea and vomiting in 30% patients [16]. There are no published trials using the presently recommended 3-day anti-emetic regimen for patients receiving single dose CY 4gm/m^2 for PBSC mobilization. This phase 2 study was designed to investigate the efficacy of AP in this setting.

Methods

Between May 2005 to June 2009, 40 patients were enrolled, five of whom were not evaluable for response. This two-stage phase 2 trial was registered in the clinicaltrials.gov database (NCT00293384). The study was conducted in accordance with the declaration of Helsinki at Karmanos Cancer Institute, Detroit, MI after approval by the Wayne State university Institutional Review Board. Patients that were proceeding to autologous stem cell transplant within this time period were presented this protocol. The patients were allowed to choose to participate in the trial or continue with the standard of care approach to stem cell collection.

Inclusion Criteria

Adults (age >18 years) scheduled to undergo autologous PBSC mobilization using high-dose CY (4 g/m^2) were eligible for the study. Patients were required to have South-West Oncology Group (SWOG) performance status 2 and adequate organ function to undergo autologous HSCT. Patients receiving warfarin $>1\text{mg}$ per day, reporting 5 alcohol drinks per day for last a year, requiring chronic systemic steroids or anti-emetics use were excluded. Patients taking any of the following medications: oral contraceptives (except for the indication to stop menses), tolbutamide, phenytoin, midazolam, ketoconazole, rifampin, paroxetine, and diltiazem were excluded. The patient characteristics are summarized in Table 1.

Pre-treatment Evaluation

All patients were asked to detail any baseline nausea, which included: 1) Number of emetic episodes that day, and 2) Nausea on visual analog scale (0–100mm) with zero being no nausea [17].

Treatment

Patients received granisetron hydrochloride 1 mg oral or intravenous (IV) along with oral dexamethasone 10 mg and oral AP 125 mg, followed 1 hour later by CY 4gm/m^2 IV administered over 90–120 minutes on day 1. On days 2 and 3, AP 80mg was given once daily to all the patients (Figure 1). No rescue medication use was allowed.

Definitions

Nausea and vomiting were assessed in two different time periods: 0–24 hours was defined as the ‘acute emetic phase’ and the 25–120 hours period was defined as ‘delayed phase’. Complete response (CR) was defined as no emetic episodes and use of no rescue medications. Partial response was 1–2 emetic episodes and no rescue medications. Response failure was defined by more than 2 emetic episodes and/or use of rescue medications. Visual analogue scale (VAS) [17], $>25\text{ mm}$ suggested severe nausea, while 5–25 mm reflected mild nausea. Emesis was defined as one or more episodes of vomiting (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents), distinct episodes being defined as those separated by at least 1 min.

Assessments

Patients who received all three doses of AP were monitored for 30 days after CY and AP administration. During the first 5 days (120 hours) after initiation of chemotherapy, patients recorded the time and date of vomiting episodes in a diary. Daily assessments of nausea were also noted using a 100 mm visual analog scale (VAS). If rescue anti-emetic therapy was taken, patients recorded the name of rescue medication along with date and time of administration. On day 2, Mesna was discontinued. A follow-up evaluation for toxicities and laboratory chemistries (including LFTs) was also performed on day 2. Fifth and seventh day evaluations were done by phone. Day 30 (+/- 7 days) visit was scheduled as an outpatient if the patient was not hospitalized for autologous HSCT. Due to lack of data there were theoretical concerns for potential drug interaction between AP and CY. At the time of trial design there was dearth of pharmacokinetic data regarding AP and CY combination and its potential effect on quality of PBSC collection. Therefore, we were required as per the investigational new drug (IND) application to monitor stem cells yield and neutrophil/platelet engraftment to detect any concerning negative effect on the PBSC collection.

Statistical analysis

Study Design—The study was designed as a Simon optimal two-stage, phase II study to distinguish a response rate of $p_1=65\%$ from that of $p_0=45\%$ with 85% statistical power testing and 10% type I error rate, with the constraint that the total sample size not exceed 40 patients. The first stage of the study required accrual of 18 response-evaluable patients. If there were 8 or fewer complete responses, then the study was to terminate at stage I. If there were 9 or more complete responses, the study was to continue to stage II by enrolling an additional 17 patients for a total of 35. The null hypothesis would be rejected if there were 20 or more responses among the 35 evaluable patients.

Statistical Analysis—One-sided binomial tests were used to evaluate statistical significance of the difference between observed proportions and hypothesized proportions for each of the endpoints. Adjustment for multiple comparisons was made in case of 5 tests of the proportion of individuals experiencing no more than mild nausea.

End-Points—The primary end-point of study was control of acute vomiting, during the first 24 hours after CY administration. The secondary endpoints were a) control of delayed vomiting, b) control of nausea, defined as no more than mild nausea, i.e. nausea score of 25 mm or less on the visual analog scale, during the first five days following CY administration and c) Toxicity, defined as occurrence of any grade 3–5 toxicity related to AP. The National Cancer Institute Common Toxicity Criteria (NCI CTC Version 3)(18) was used to grade all adverse events and assign any attribution of these events to the study treatment regimen. The tertiary endpoint was successful CD34+ stem cell mobilization, defined as collection of at least 2×10^6 CD34+ cells / kg actual body weight. Absolute neutrophil count (ANC) recovery was defined as an ANC of $0.5 \times 10^9/L$ ($500/mm^3$) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first three consecutive laboratory values where the ANC is $0.5 \times 10^9/L$. Platelet recovery was defined according to Center of International Blood and Marrow Transplantation Research (CIBMTR) criteria as no platelet transfusions in the previous seven days, and the first of three consecutive laboratory values obtained on different days that are $20 \times 10^9/L$.

Results

Patient characteristics

Most response-evaluable patients were male (57%) and Caucasian (87%) with a median age of 48 years (range 23 – 64). Multiple myeloma (MM) was the most common underlying

malignancy (19/35, 54%); followed by non-hodgkin's lymphoma (NHL) (11/35, 31%), hodgkin's disease (HKD) (4/35, 11%) and acute promyelocytic leukemia (APL) (1/35, 3%). All patients received CY 4gm/m² and filgrastim (10–16mcg/kg/d) for PBSC mobilization (Table 1)

Results and Outcomes

In the first stage, 22 patients were enrolled of whom 18 were response-evaluable. Of the 4 participants who were not response-evaluable: one refused the medication, one was not compliant and never received a HSCT and two others reported baseline nausea (an exclusion criterion). Ten out of 18 response-evaluable patients (56%) reported complete response (Table 2). The study then progressed to stage 2 and an additional 17 patients were enrolled.

Primary Endpoint—Altogether, 20/35 evaluable patients (57%) met the criterion for the primary endpoint (Table 2), defined as no vomiting episodes and no use of rescue medication during the first 24 hours, thus achieving the critical threshold number for success i.e. 19 of 35 patients. The null hypothesis that the emesis control rate was 45% or less was rejected at $p=0.10$ (one-sided).

Secondary Endpoints—A key secondary end-point was control of delayed vomiting defined as no vomiting episodes during days 2 through 5 and no rescue medications. Twenty two of 35 response evaluable patients (63%) reported no episodes of delayed vomiting, exceeding threshold for the rate of control of delayed vomiting greater than 30% ($p<0.001$). In totality, 20 out of 35 patients did not experience any acute or delayed emesis and did not use any rescue medications.

On the other hand, we were not able to reject the null hypothesis ($p=0.64$) that the rate of adequate nausea control is at least 50%; 31 out of 35 evaluable patients completed the 5 day nausea diary; only 15 (43%) patients reported no more than mild nausea during all 5 days of this period. However, median days of only mild nausea were 4 (inter-quartile range 3–5). (Figure 2)

Tertiary Endpoint—Nearly all (33/35, 94%) of response-evaluable patients had successful CD34⁺ stem cell mobilization supporting the hypothesis that the rate of successful mobilization is at least 50% ($p<0.001$). For the 35 evaluable patients, the median number of days to neutrophil engraftment was 11 days (range 9–13 days) and median days to platelet engraftment were 20 (range 0–42 days). The engraftment of neutrophils and platelets was within clinically acceptable range.

Tolerability

No grade 3 or higher toxicities definitely related to AP were noted for any patients, in accord with the hypothesis that the rate is $< 20\%$ ($p<0.001$). The incidences of laboratory and clinical adverse events were consistent with a population of patients with cancer who were undergoing high-dose chemotherapy and autologous HSCT (Table 3). Other than nausea and vomiting, fatigue, diarrhea, febrile neutropenia, headaches and hiccups were the most commonly noted adverse effects. No patient discontinued treatment due to laboratory events. No treatment-related mortality has been noted.

Discussion

Multiple phase 3 studies evaluating patients with solid tumors have demonstrated the benefit of AP in the prevention of CINV from HEC, particularly cisplatin-containing regimens, when combined with corticosteroid and 5-HT₃ antagonist [7, 8, 19 and 20]. However, high-

dose CY induces a more prolonged pattern of emesis which differs from cisplatin containing regimens [16]. Despite standard anti-emetic therapy late onset of nausea, vomiting and the high incidence of CINV on days 2–3 results in significant morbidity, hence necessitating a search for more potent anti-emetic drugs combination.

The intent of our study was to assess CINV after treatment with AP, 5-HT₃ antagonists and adjusted dose dexamethasone in patients receiving high dose CY (4 gm/m²) for PBSC mobilization. Our results show that the AP regimen protects nearly two-thirds of patients from emesis, avoiding further use of anti-emetics during the 5 days after CY administration. Twenty out of 35 patients met the primary end-point of preventing CINV within the first 24 hours. Because patients were considered treatment failures if they either vomited or took any antiemetic rescue medication to alleviate nausea, this response endpoint not only reflects control of emesis but also indirectly reflects adequate control of nausea.

In our study, the control of delayed emesis was more pronounced as compared to the acute phase (a difference of 6 percentage points). It has recently been demonstrated that while serotonin-dependent mechanisms dominate in the acute phase, NK-1-dependent mechanisms dominate in delayed-phase vomiting [21]. Since the latency of emesis post- CY is long (10.5 hours) and there is little or no elevation of urinary 5-hydroxyindoleacetic acid (5- HIAA, the main metabolite of 5-HT) in patients given high-dose CY [22], the argument for the use of an anti-emetic regimen for 3–5 days with NK-1-dependent mechanism seems valid.

Adequate nausea control was not reached in our study as 15 out of 31 patients who completed the symptom diary reported having mild nausea. As discussed by previous studies as well [19, 23], this may suggest that the neurokinin-1 receptor antagonists have less impact on the chemotherapy-induced nausea, more specifically CY-evoked nausea. The control of nausea can lag behind the control of vomiting, perhaps because of the difficulty of measuring this subjective symptom and the possibility that patients confuse nausea with other symptoms like anorexia, fatigue or fever. This might be a plausible explanation for over or under reporting of this subjective symptom making accurate assessment difficult on a self reporting diary.

We are cognizant of the potential interaction between AP and other medications eliminated via CYP3A4. While we agree that the lack of pharmacokinetic assessments is a limitation of our study, it is important to note that multiple studies in the recent past have failed to establish any significant impact of AP on chemotherapy-related toxicity [6, 7, and 23]. CY must be activated by CYP3A4, hence the possibility that AP could decrease its activation, leading to decreased anti-tumor efficacy. However, no negative impact on stem cell harvest or neutrophil/platelet engraftment was noted in the present study. This trial demonstrates an important safety finding for using AP in combination with CY for PBSC collections. This can be a feasible option for patients with difficulty to mobilize PBSC and especially multiple myeloma patients with prolong exposure to lenalidomide. All study patients were monitored closely for any signs of increased CY toxicity, which was not evident in evaluable patients.

The results of a randomized, prospective double-blind phase 3 trial studying the safety and efficacy of AP for CINV control in patients receiving highly emetic high dose preparative regimens prior to hematopoietic stem cell transplant were recently presented at 2009 annual meeting of American Society of Hematology [24]. Using 179 randomized study subjects, Stiff P et al and his colleagues have demonstrated a significant difference in CR rate (primary endpoint) in favor of AP: 81.9% versus 65.8 % for those receiving placebo with 48.9% versus 14.6% respectively meeting the endpoint for entire study period (p<0.001). AP

had no negative impact on neutrophil and platelet engraftment. Additionally, AP was noted to have no effect on progression-free and overall survival.

Conclusions

This trial lends evidence to support the use of AP for patients receiving high-dose CY for PBSC mobilization. The addition of AP to an anti-emetic regimen of a 5-HT₃ antagonist plus dexamethasone improved the control of CINV associated with highly emetogenic CY-based chemotherapy. The AP regimen was well tolerated and had no adverse impact on PBSC mobilization using high-dose CY. The data from this study provides sound clinical rationale for using the AP combination regimen for patients receiving high-dose CY for HSCT mobilization and may be with high dose CY containing conditioning regimens.

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Figure 1.
Schema

Figure 2.

Box plots of analog nausea scores by day following CY administration. Boxes enclose middle 50% (IQR) of observations, white line indicates median. Whiskers extend to cover points within 1.5 x IQR above the 75% percentile, dots indicate outlying observations. The red line indicates the upper limit of mild nausea.

Table I

Patient characteristics at baseline (n=35)

Variable	Patients N
Age(years), median (range)	48 (23–64)
Gender	
Male	20
Female	15
Race	
Caucasians	30
African Americans	4
Others	1
Diagnosis	
Acute Promyelocytic Leukemia	1
Hodgkins Disease	4
Non Hodgkins Lymphoma	11
Multiple Myeloma	19

Table II**Results at the End of Stage 2**

	Endpoint	Null Hypothesis	Freq (%)	Signif.
Primary	24 hour control of emesis without rescue medication	$\leq 45\%$	20/35 (57%)	0.10
Secondary	Control of delayed emesis days 2–5	$\leq 30\%$	27/35 (77%)	<0.001
Secondary	No more than mild nausea days 1–5	$\leq 50\%$	15/31 (48%)	0.64
Secondary	Grade 3 or greater toxicity	$\geq 20\%$	0/35 (0%)	<0.001
Tertiary	Successful CD34+ stem cell mobilization	$\leq 50\%$	34/35 (97%)	<0.001

Table III

Adverse events after high dose cyclophosphamide (<Grade 3)

Most commonly reported clinical adverse events	Patients (%)
Nausea	68.5
Vomiting	40
Fatigue	51
Diarrhea	28.5
Febrile Neutropenia	20
Headache	20
Hiccups	20
Dyspnea	14.3
Constipation	11.4
Weight gain	11.4