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ORIGINAL ARTICLE

A phase II open-label study of aprepitant as anti-emetic prophylaxis in patients with acute myeloid leukemia (AML) undergoing induction chemotherapy

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Abstract

Despite the widespread use of 5-HT_3 antagonists as anti-emetic prophylaxis in patients with acute myeloid leukemia (AML) receiving induction chemotherapy, nausea and vomiting persist in many cases. We performed a Phase II single-arm study evaluating the use of aprepitant on days 1–5, in combination with a 5-HT antagonist on days 1–3, in AML patients undergoing induction chemotherapy with daunorubicin on days 1–3 plus cytarabine, given as a continuous infusion, on days 1–7. This was compared to a retrospective cohort of AML patients that received the same chemotherapy regimen with a 5-HT antagonist but without aprepitant. The cumulative incidence of vomiting/retching by the end of day 5 was significantly lower in the aprepitant vs. the control group (26.3 vs. 52.8%, $p = 0.013$). The cumulative incidence of nausea by the end of day 5 was 61% in the aprepitant group vs. 75% in the control group. The total use of supplemental anti-emetics on days 2–5 was also significantly lower in the aprepitant group ($p = 0.01$). In contrast, the cumulative incidence of vomiting/retching by the end of day 8, the incidence of vomiting/retching on days 6–8, and the use of anti-emetics on days 6–8, were not significantly different between the two groups. The results suggest that the use of aprepitant may be associated with a lower rate of emesis during aprepitant dosing days, but not afterward. However, this requires confirmation in a randomized trial.

Keywords Acute myeloid leukemia · Anti-emetics · Chemotherapy · Neurokinin inhibitors

Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains a major adverse effect of chemotherapy. Agents are divided into those regarded as highly emetogenic (e.g., high-dose cisplatin, dacarbazine) which produce emesis in > 90% of patients; moderately emetogenic (e.g., most anthracyclines, high dose cytarabine) which produce emesis in 30–90% of patients; and mildly emetogenic, producing emesis in < 30% of patients [1].

For control of early CINV (within 24 h of treatment) in cancer patients receiving moderately or highly emetogenic drugs, the most widely used prophylactic regimens include a 5-HT_3 (serotonin receptor) antagonist, such as granisetron, ondansetron, or dolasetron. This is often combined with dexamethasone to produce optimal efficacy. While these prophylactic regimens have been shown to reduce the incidence of early CINV, they have been less effective in controlling delayed CINV [2], defined as nausea and vomiting occurring > 24 h post-chemotherapy. CINV adversely impacts patients' quality of life [3] and has been regarded by patients as among the most feared symptoms associated with chemotherapy [4].

Recently, a new class of agents has been developed which target the NK_1 (neurokinin) receptor. The first agent of this class which has become available is aprepitant. This agent exerts its anti-emetic effect by interfering with the binding of substance P to neurokinin-1 receptors, which are located in

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several regions of the brain involved with nausea and vomiting. A number of randomized trials have demonstrated the efficacy of aprepitant in reducing the incidence of both acute and delayed CINV in patients receiving highly emetogenic chemotherapy, when given in combination with a 5-HT_3 receptor antagonist and dexamethasone [5–8]. Aprepitant has also been shown to significantly reduce the incidence of vomiting in patients with breast cancer receiving a moderately emetogenic regimen consisting of cyclophosphamide plus either doxorubicin or epirubicin [9].

Standard frontline chemotherapy for acute myeloid leukemia (AML) consists of cytarabine, given as a 7-day continuous infusion at 100–200 mg/m^2/day, plus 3 days of anthracycline, most commonly daunorubicin (3 + 7 regimen). Although varying doses of daunorubicin have been used, the dose of 60 mg/m^2 daily × 3 is currently widely used by many large centers and cooperative groups [10, 11]. This regimen is generally administered on an inpatient basis from the start of treatment until hematologic recovery, which usually takes approximately 4 weeks. Daunorubicin at this dose is regarded as a moderately emetogenic drug, while cytarabine is only mildly emetogenic at the doses used [1].

There are limited data regarding the efficacy of aprepitant in AML therapy. A phase II randomized study found that aprepitant, when added to high-dose cytarabine-based chemotherapy (at doses of ≥1 g/m^2) plus ondansetron, was associated with a trend toward a lower frequency of nausea and a lower use of rescue mediations, compared to ondansetron alone; however, these effects did not reach statistical significance [12]. However, there are no published studies evaluating the role of aprepitant as prophylaxis in patients receiving 3 + 7 induction therapy. We now report results of a phase II study evaluating the use of aprepitant, when added to a 5-HT_3 receptor antagonist, as anti-emetic prophylaxis using this regimen.

Methods

This was a prospective phase II open-label single-center study evaluating the use of aprepitant, added to standard anti-emetic prophylaxis, in patients receiving frontline induction chemotherapy for AML, using a 3 + 7 schedule. The study was conducted on the inpatient leukemia units at Princess Margaret Cancer Centre, Toronto, Canada, from January 2012–June 2013. Eligible subjects included patients age 18 and over with previously untreated de novo or secondary AML (any subtype except acute promyelocytic leukemia). Other inclusion criteria included serum bilirubin ≤ 1.5 times the upper limit of normal (ULN), aspartate transaminase, and alanine transaminase ≤ 2.5 times ULN and serum creatinine < 200 μmol/L. Exclusion criteria included uncontrolled nausea or vomiting (grade 2 or higher) within 48 h prior to the start of induction chemotherapy, known hypersensitivity to granisetron, ondansetron or aprepitant, an inability to swallow or absorb oral medications, or use of an alternate chemotherapy regimen. Prohibited concomitant treatments included strong CYP3A4 inhibitors or substrates, systemic corticosteroids, radiotherapy, or other chemotherapeutic or investigational agents. All subjects provided written informed consent.

Induction chemotherapy consisted of cytarabine 200 mg/m^2 (100 mg/m^2 for patients age 60 years and over) as a 7-day continuous intravenous (IV) infusion, plus daunorubicin 60 mg/m^2 by slow IV push once daily on days 1–3. All patients received either granisetron 1 mg IV ($N = 22$) or ondansetron 8 mg IV ($N = 19$) on days 1–3, given approximately 1 h prior to each dose of daunorubicin. Aprepitant was given at a dose of 125 mg orally (PO) on day 1 and 80 mg PO on days 2–5 inclusive; doses on days 1–3 were given prior to each dose of daunorubicin. Supplemental anti-emetics were given as required (PRN), at the physician's and nurse's discretion, as per standard practice, although additional aprepitant was not permitted. Supplemental anti-emetics utilized included metoclopramide, prochlorperazine, dimenhydrinate, nabilone, or additional granisetron or ondansetron. Other supportive care measures, including tumor lysis prophylaxis and antibiotic use, were administered as per standard institutional policy. Anti-fungal prophylaxis consisted of fluconazole 400 mg PO daily starting on day 6.

The evaluation period extended from the start of day 1 of chemotherapy to the end of day 8. Evaluations consisted of review of nursing records, documenting any episodes of nausea/vomiting, and a patient self-assessment form which was completed on a daily basis, specifying such episodes. The use of supplemental anti-emetics was determined by nursing and pharmacy records. The primary outcome measure was the cumulative incidence of vomiting and/or retching from the start of chemotherapy day 1 through the end of day 5. Secondary outcomes included the daily and cumulative incidence of nausea from days 1 to 8 inclusive, the daily and cumulative incidence of vomiting/retching from days 1 to 8 inclusive, the total number of patients requiring supplemental anti-emetics each day, and the total number of such doses administered daily, on aprepitant dosing days and for the entire 8-day period.

As a comparator, a retrospective analysis was performed on a cohort of 36 consecutive AML patients who received the same AML induction regimen, and the same anti-emetic prophylaxis schedule using granisetron or ondansetron, but without aprepitant, at Princess Margaret Cancer Centre between July and Dec 2009. Data regarding nausea and vomiting were obtained from the nursing and physician inpatient records and

correlated with pharmacy records documenting the use of anti-emetics, over 8 consecutive days from the start of treatment. Patient self-assessment forms were not used in the retrospective cohort.

Statistical considerations The sample size was initially calculated using Simon's optimal two-stage design to test the null hypothesis that the rate of vomiting is $\geq 50\%$ (the incidence determined in the retrospective cohort—see below) by the end of day 5 (primary outcome measure) versus the alternative hypothesis that the rate of vomiting was $\leq 32.5\%$. In the first stage, 27 subjects were to be enrolled; if no vomiting was seen in at least 15 subjects, the study was to proceed to enroll a total of 82 subjects. The treatment was to be considered effective if no vomiting was seen in at least 50/82 subjects (power set at 90%, significance level at 0.05). At the interim analysis, no vomiting/retching was seen in 22/27 subjects; given the low observed rate, it was subsequently decided to reduce the sample size to 42 subjects, as it was estimated that this sample size would be sufficient to reach the primary endpoint.

Descriptive statistics were used to describe patient demographics such as gender and age. Comparisons between baseline features, rates of nausea/vomiting, and supplemental anti-emetic use were performed on each day by chi-square or Fisher's exact test as appropriate. In addition, in order to evaluate the impact of aprepitant dosing, a linear mixed modeling (that accounts the collinearity of repeated measures of each patient on days 1–8) was used for comparing the combined incidence of vomiting/retching and the use of supplemental anti-emetics on aprepitant dosing days 2–5 and on post-dosing days 6–8, respectively, in the aprepitant vs. control groups. All *P* values were two-sided. Results were considered significant if $p < .05$. Statistical analyses were performed using SAS version 9.4 of the SAS system for Windows (Copyright 2002–2012 SAS Institute, Inc., Cary, NC). Grading of vomiting was done using Common Terminology Criteria for Adverse Events (CTCAE), version 4.

Results

A total of 42 patients were enrolled; of these, one did not receive aprepitant (for reasons that were unclear), leaving 41 subjects who received treatment on study. There were 18 females and 23 males; the median age was 56 years (range 22–78). Of these, 38 subjects had nursing and patient self-assessments for nausea and vomiting completed; the other three were excluded from this part of the analysis due to missing data for at least part of their course. However, information for the use of supplemental anti-emetics was available for all 41 subjects.

The median age of the historical control group was 57 years (range 29–82), with 16 females and 20 males; these were not significantly different than in the aprepitant study cohort. In both the aprepitant and control cohorts, there was no significant difference in the rates of vomiting/retching in the older (> age 60) vs. younger age groups, nor was there any difference according to the type of 5-HT_3 antagonist used (data not shown).

The cumulative incidences of nausea and vomiting/retching at the end of day 5 and day 8 are shown in Table 1. As the nausea rates in the control group were determined only by review of the patients' charts (since there were no patient self-assessments done), there was no direct compassion between the two cohorts for this parameter. As shown, there was a significantly lower cumulative incidence of vomiting/retching in the aprepitant group, as compared to the control group, by the end of day 5. However, by the end of day 8, this difference was not reaching statistical significance. The daily incidences of vomiting/retching in both the aprepitant and control groups are shown in Fig. 1. There was a trend toward lower rates of vomiting/retching in the aprepitant group vs. the control group on each of days 2–5; conversely, there was a trend toward a higher incidence in the aprepitant group on day 6 (i.e., 1 day after receiving the last dose of aprepitant). However, none of these daily differences reached statistical significance. Using a linear mixed effects model that accounts the repeated data of each patient daily, combining aprepitant dosing days 2–5 and post-dosing days 6–8, there was a significantly lower cumulative incidence of vomiting/retching in the aprepitant group on days 2–5, compared to the control group (odds ratio 0.46, 95% confidence intervals [CIs] 0.25–0.85, $p = 0.013$). In contrast, the cumulative rates on days 6–8 were not significantly different between the two groups (odds ratio 1.50, 95% CI 0.68–3.30, $p = 0.31$). In terms of severity of vomiting in the aprepitant cohort, six cases were grade 2 (5 of these during aprepitant dosing days); the remainder were grade 1. In the control group, three cases were grade 2 (all during Days 1–5), while the remainder were grade 1.

The percentage of patients receiving at least one dose of supplemental anti-emetics, and the mean number of doses of supplemental anti-emetics administered per patient, in the two groups is shown in Fig. 2. As shown, there was a trend toward a lower use of supplemental anti-emetics in the aprepitant cohort on each of days 2–5, while the use was comparable between the two groups on day 6. As none of the daily comparators reached statistical significance (possibly due to small numbers), a linear mixed-effects model was again performed, combining the total usage of supplemental anti-emetics during the aprepitant dosing days 2–5 (excluding day 1 when rates were very low) and during the post-dosing days 6–8 inclusive. Combining these days, the percentage of patients receiving supplemental anti-emetics was significantly lower on days 2–5 in the aprepitant group vs. the control group (odds ratio 0.56, 95% CI 0.35–0.89, $p = 0.01$). In contrast, the proportion was not significantly different between the two groups on days 6–8 (odds ratio 0.72, 95% CI 0.42–1.23, $p = 0.23$).

Table 1 Cumulative incidences of nausea and vomiting/retching in the group that received aprepitant, and in the historical control group. As the indicators used to determine nausea were different between the two groups, these rates were not compared statistically. *N.D.* not done

Characteristic *n* (%)	Aprepitant cohort (*n* = 38)	Historical Cohort (*n* = 36)	*P* value
Cumulative incidence of vomiting/retching by end day 5	10 (26.3%)	19(52.8%)	0.02
Cumulative incidence of nausea by end day 5	23 (60.5%)	27 (75.0%)	N.D.
Cumulative incidence of vomiting/retching by end day 8	13 (34.2%)	20 (55.6%)	0.065
Cumulative incidence of nausea by end day 8	26 (68.4%)	30 (83.3%)	N.D.

Discussion

Although 5-HT_3 antagonists have had a major impact on nausea and emesis in patients undergoing 3 + 7 induction chemotherapy for AML, our data in the control population indicate that most patients still experience ongoing nausea, and approximately one-half will experience at least one episode of vomiting/retching, most prominently in the first 5 days. Since the anthracycline administered in the first 3 days is the more emetogenic of the two agents, it is therefore likely that early and delayed onset anthracycline-induced nausea/vomiting is the major culprit.

Although not a randomized study, our results suggest that the addition of aprepitant to the 5-HT_3 antagonist was associated with a favorable impact on vomiting/retching over the first 5 days, with a 50% reduction in the cumulative incidence by the end of day 5; therefore, the primary endpoint of the study was reached. This was associated with a lower overall rate of breakthrough anti-emetic use on these days. However, there appeared to be a rebound spike in emesis on the day following completion of the aprepitant, suggesting that this effect only lasted while this drug was being administered. The reason why this incidence on day 6 appeared to be higher than in the control group is unclear; it may be that the increased use of supplemental anti-emetics in the control group was able to more effectively control this complication beyond day 5. In addition, the use of breakthrough anti-emetics on days 6–8 was comparable between the two groups. Our data suggest that, if aprepitant used, its duration should be extended beyond day 5 to attempt to extend its anti-emetic effect and prevent a rebound increase in emesis. However, it is unclear whether this would be effective. Although aprepitant adds further cost (approx. $32.50 Can. per dose), this would be at least partly offset by a reduced use of supplemental anti-emetics.

The influence of aprepitant on nausea control was less apparent. Other studies have also noted a lesser impact of aprepitant on control of nausea [13, 14], as the latter may be more affected by other mechanisms such as psychological factors. The 60% rate of nausea by the end of day 5, and the ongoing use of supplemental anti-emetics over this time period, suggests that control of nausea was less prominent with this agent. However, it is difficult to ascertain whether control of nausea was better than in the control group, since the parameters used to measure this endpoint were different. It is possible that the additional use of patient self-assessment forms in the aprepitant group may have inflated the rate, and that, conversely, the rate of nausea was under-recognized in the control group by not using this self-assessment. An additional limiting factor in this analysis is that, since this was not a blinded study, we cannot exclude the possibility of a placebo effect on this subjective endpoint in the aprepitant group, which may have lowered the observed rate. We also did not collect data on the severity of nausea; this would have to be addressed in any future studies.

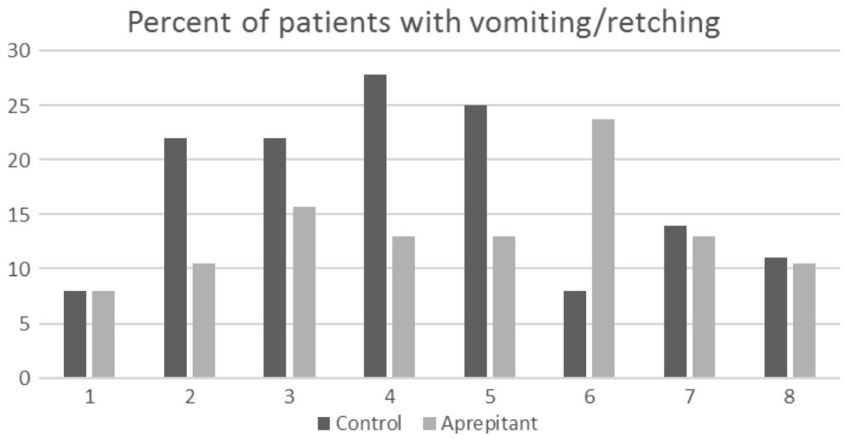

Fig. 1 Daily rates of vomiting/retching in the group that received aprepitant (*n* = 38) and in the historical control group (*n* = 36)

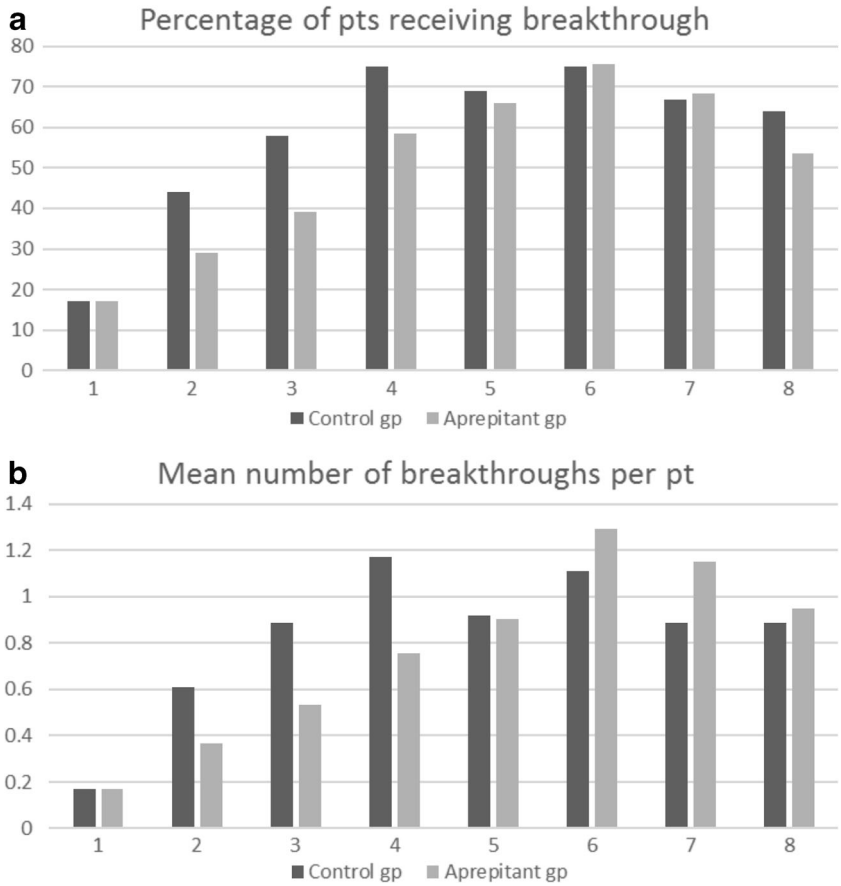

Fig. 2 Use of supplemental anti-emetics on a daily basis. **a** Percentage of patients receiving at least one dose of supplemental anti-emetics in each group. **b** Mean number of doses of supplemental anti-emetics administered per patient in each group

A recent small study using aprepitant in hematologic malignancies suggested the benefit was limited to patients receiving concomitant corticosteroids [14]. At our center, corticosteroids have not been used as anti-emetic prophylaxis in AML, partly due to its immunosuppressive effects, but also due to previously published in vitro data demonstrating that corticosteroids may protect AML blasts from cytarabine-induced cytotoxicity [15]. However, a recent AML study suggests that dexamethasone may actually enhance cytotoxicity and lower relapse rates, at least in some cases [16].

Although the findings suggest that aprepitant improves the control of emesis in the first 5 days with this regimen, it cannot be regarded as conclusive due to the uncontrolled nature of this study. However, this study supports the need for a double-blind placebo-controlled randomized study to confirm the efficacy of aprepitant in induction chemotherapy and assists with designing a proper sample size. Our study also suggests that aprepitant should be considered for a longer time period, perhaps for the entire 7 days of the cytarabine infusion, in such a study. Nevertheless, this study indicates that, even with the use of aprepitant combined with a 5-HT_3 antagonist, control of both nausea and vomiting remain suboptimal, and further prophylactic measures, such as the use of concomitant dexamethasone, should be evaluated.

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Compliance with ethical standards

The study received prior ethics approval by the local institutional review board and was registered at Clinicaltrials.gov (NCT01334086).

Conflict of interest The authors declare that they have no conflict of interest.

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