

Effect of increase in duration of aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of anthracycline/cyclophosphamide chemotherapy: A randomized, crossover, clinical trial

Negah Chaabi Ahvazi, Simin Hemati, Mohamad Mohamadianpanah¹

Department of Radiotherapy and Oncology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, ¹Colorectal Cancer Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Background: Aprepitant is one of the effective antiemetic drugs that usually used for a period of 3 days for prevention of anthracycline/cyclophosphamide (AC) induced nausea and vomiting. However, many patients still experience nausea and vomiting on days 3–5. The aim of this study was to evaluate the effect of an increase in duration of aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving AC chemotherapy.

Materials and Methods: It was a randomized, crossover, controlled clinical trial. Women with breast cancer and scheduled to receive AC regimens were enrolled in this study. Enrolled patients were randomized into two groups. Group I received 3 days regimen of aprepitant in the first course of AC regimen chemotherapy and 6 days regimen of aprepitant in the second course; Group II received 6 days regimen followed by 3 days regimen. For nausea and vomiting assessment, we used Eastern Cooperative Oncology Group questionnaire.

Results: Forty-nine patients were enrolled in this study. Sixty-three percent achieved a complete response with 6 days aprepitant regimen compared with 39% with 3 days regimen ($P < 0.001$). Ten percent had at least one vomiting episode during the 6 days regimen versus 15% with 3 days regimen ($P = 0.034$). Nausea was significantly more severe in 3 days regimen of aprepitant than in 6 days regimen.

Conclusion: Increase in the duration of aprepitant consumption through 6 days resulted in significantly better prevention of nausea and vomiting than 3 days consumption for women receiving AC chemotherapy.

Key Words: Anthracycline, aprepitant, chemotherapy, cyclophosphamide, drug-related side effects, nausea, vomiting

Address for correspondence:

Dr. Simin Hemati, Department of Radiotherapy and Oncology, Isfahan University of Medical Sciences, Hezarjerib Avenue, Isfahan, Iran. E-mail: hemati@med.mui.ac.ir

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) can be one of the most distressing problems for patients.

This side effect impairs patients' quality of life, decline cognitive functions, and physical ability and may eventually affect the patient's desire to continue further

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chemotherapy.^[1,2] The mechanisms of CINV seems to be depend on the cellular injury induced by chemotherapy, which may release neurotransmitters.^[3] Dopamine and serotonin (5-hydroxytryptamine [5-HT]) are the major excitatory neurotransmitters that are involved in emesis.^[3]

Several patient-related risk factors for CINV are generally assumed, including gender, age, alcohol use, and history of motion sickness.^[4] Patients <50 years old and women are more likely to suffer from CINV.^[5] Although, chemotherapy agents are vary in degrees of emetogenic potential and combinations of emetogenic agents may have additive effects on the overall CINV.^[6]

The combination of anthracycline/cyclophosphamide (AC) chemotherapy is a particularly high risk for inducing nausea and vomiting and considered as being highly emetogenic.^[7,8]

Strategies for antiemetic prophylaxis have developed in recent years.^[9,10] Some antiemetic guidelines for patients receiving highly emetogenic chemotherapy (HEC) recommend the use of the oral neurokinin-1 (NK1) receptor antagonists as part of a routine regimen that also includes a corticosteroid and a selective 5-HT₃ receptor antagonist.^[11-13] The incidence of CINV in patients receiving HEC, including breast cancer patients treated with 5-HT₃-receptor antagonists is approximately 50%.^[14]

Aprepitant is the first commercially available drug of a new class of NK1 receptor antagonists with little or no affinity for other NK receptors.^[15,16] Approved by Food and Drug Administration in 2003 for the prevention of chemotherapy-induced emesis and usually administered for a period of 3 days.^[17] Recent studies reveal the efficacy of aprepitant in preventing CINV in patients who received AC and nonAC-based HEC regimen.^[18-20]

However, despite these results, many cancer patients still experience CINV,^[18,21] also the trend has now been reversed with increasing nausea and vomiting on days 3–5. Hence, there is clearly a need for more effective prevention of CINV in patients receiving HEC on delay phase, especially in a patient, who is particularly susceptible to these symptoms such as women.

Here, we present the study of aprepitant duration for the management of nausea and vomiting associated with AC-containing chemotherapy in women with breast cancer. We hypothesized that addition of aprepitant duration from 3 to 6 days would improve emetic symptoms in women receiving AC – based chemotherapy for breast cancer.

MATERIALS AND METHODS

Study design

This study was a randomized, crossover, controlled clinical trial (IRCT2015040121574N1), and designed to evaluate the effect of increase in duration of aprepitant usage from 3 days to 6 days on the prevention of nausea and vomiting in women receiving combination of AC chemotherapy. This trial was conducted in referral university hospital in Isfahan (Iran's third largest city, located in the center of Iran), Iran. The Medical Ethics Committee of Isfahan University of Medical Sciences has approved the study design, protocols, and informed consent procedure (the ethical code was 393449).

Participants

Fifty patients with breast cancer were enrolled in this study through convenience sampling method. We included patients who were under 50 years of age, diagnosed with breast cancer and scheduled to receive four courses AC regimens. The following general exclusion criteria were considered: Previous history of gastritis, diabetes, and a brain tumor. In order to detect two-fifth standard deviation difference in the main outcome (nausea severity score), with $\alpha = 0.05$ and power = 80%. We considered 10% attrition rate and the final sample size was estimated 50 patients (25/group). Patients served as their own controls for study cycles.

Intervention

Enrolled patients were randomized to 1 of 2 groups. According to the crossover design of the study, Group I received Treatment A (3 days regimen) in the first course of 1-day AC regimen chemotherapy and Treatment B (6 days regimen) in the second course of 1-day AC regimen chemotherapy; Group II received Treatment B followed by Treatment A. Treatment A (3 days regimen) consisted of aprepitant (ABITANT, Abidi, Iran) 125 mg orally plus dexamethasone 8 mg injected intravenous (IV) on day 1 followed by 80 mg dexamethasone once per day on days 2 and 3 administered orally (p.o.). Treatment B (6 days regimen) consisted of aprepitant 125 mg orally plus dexamethasone 8 mg injected IV on day 1 followed by 80 mg dexamethasone once per day on days 2 through 6 administered orally (p.o.). There was a 30-day washout between the first and second courses.

Measurement

Patients were followed from the 1st day of chemotherapy for a total of 7 days.

For nausea and vomiting assessment, we used Eastern Cooperative Oncology Group common toxicity criteria questionnaire, asking patients to answer two specific

questions about any nausea and vomiting symptoms. First question was about nausea severity on a 0–3 scale (0 = being no nausea, 1 = able to eat reasonable intake, 2 = intake significantly decreased but can eat, 3 = no significant intake) and second question was about vomiting (0 = none, 1 = 1 episode in 24 h, 2 = 2–5 episodes in 24 h, 3 = 6–10 episodes in 24 h, and 4 = >10 episodes in 24 h, or requiring parenteral support). Complete response (CR) was defined as no nausea and no episodes of vomiting during the study period.

All patients were given this questionnaire on cycle 1 and cycle 2, at baseline (prior to each chemotherapy treatment course), and after 7 days. Only patients with no symptom of nausea and vomiting (score of zero) at baseline (before chemotherapy) were eligible for entering to each cycle of this study.

Statistical analyses

All statistical analysis was performed by using SPSS version 20 (Release 2011, SPSS Inc., Chicago, IL, USA) for windows. Findings had shown as relative frequencies, mean and standard deviation. The comparisons were performed by McNemar’s tests, Wilcoxon signed-rank tests, paired Student’s *t*-test. A mixed general linear model was used to adjust for age and order of interventions (Treatment B followed by Treatment A or Treatment A followed by Treatment B) for all comparisons. All tests were two-sided, and *P* < 0.05 is considered significant. The statistical approach was based on an intention to treat.

RESULTS

A total of 50 patients were enrolled in the study. One patient declined to continue participating in the study on his decision with no reason. A consort diagram illustrates patient flow through each cycle of the study [Figure 1].

All of the participants were women with breast cancer and were free from nausea and vomiting before entering to each cycle. The mean age of the 49 subjects analyzed was 38.7 ± 6.5 years.

Thirty-one (63%) of 49 patients achieved a (CR was defined as no nausea and no episodes of vomiting) with 6 days regimen of aprepitant compared with 19 (39%) on 3 days regimen of aprepitant (*P* < 0.001) [Table 1]. Overall, 19 (38.6%) patients achieved a CR with both of two regimens, 12 (24.4%) experienced CR with 6 days regimen but not attended CR when they cross over to the 3 days regimen and 18 (37%) not achieved CR with both of two regimens [Table 1].

As present in Figure 2, 90% in the 6 days regimen of aprepitant versus 85% in the 3 days regimen of

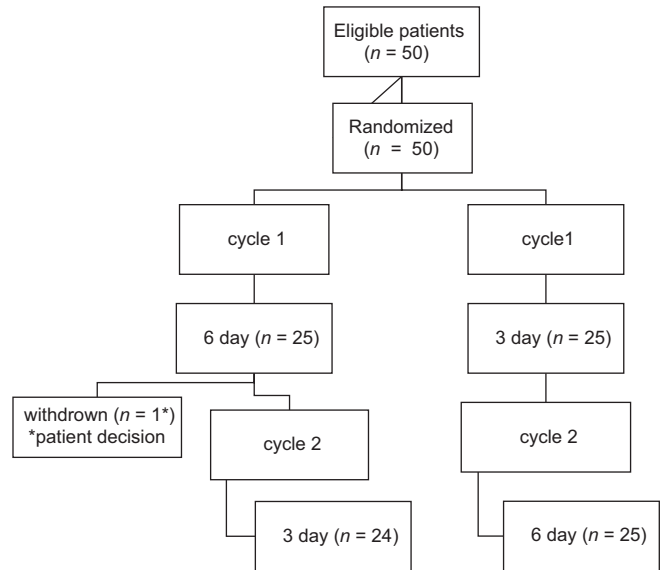


Figure 1: Flow diagram of participants through each cycle of the study

Table 1: Comparison of CR between two aprepitant regimens after crossover

6 days regimen of aprepitant	3 days regimen of aprepitant		Total (%)
	CR	Not CR	
CR	19	12	31 (63)
Not CR	0	18	18 (37)
Total (%)	19 (39)	30 (61)	49

Note: Of 31 patients achieving a CR with 6 days regimen of aprepitant, 19 subsequently attained a CR when they cross over to the 3 days regimen of aprepitant. Conversely, all of 19 CRs with 3 days regimen of aprepitant had a CR with 6 days regimen of aprepitant. McNemar’s test *P* < 0.001. CR was defined as no nausea and no episodes of vomiting. CR: Complete response

aprepitant experienced no vomiting episode. In the 6 days regimen, one vomiting episode was experienced for 10.2% of the patient compared with 6.1% in the 3 days regimen. No one experienced more than 1 episode of vomiting with 6 days regimen, but 8.2% of patient experienced 2–5 vomiting episodes with 3 days regimen. The number of vomiting episodes was significantly lower during the 6 days regimen than during the 3 days (*P* = 0.034) [Figure 2]. No one experienced more than 5 episode of vomiting during the study.

The proportion of patient that remained free from nausea in 6 days regimen was 63% compare with 39% in 3 days regimen (*P* < 0.001). Nausea was significantly more severe in 3 days regimen of aprepitant than in 6 days regimen of aprepitant [Figure 3].

The order of treatment regimens (consumption of each regimen in the first cycle or second cycle) was not affected the results of study.

Both treatment regimens were tolerable for the patient, and no one was complaining of side effects.

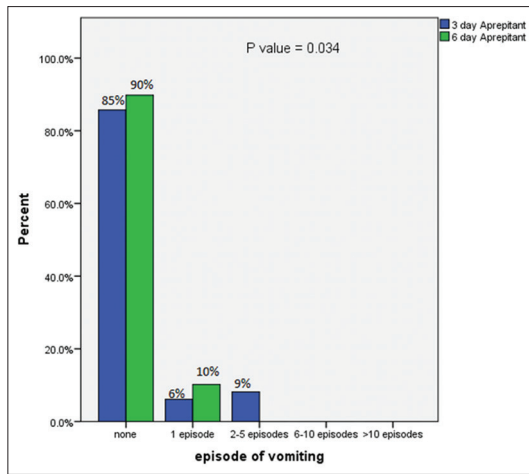


Figure 2: Percentage of patients experiencing different episode of vomiting

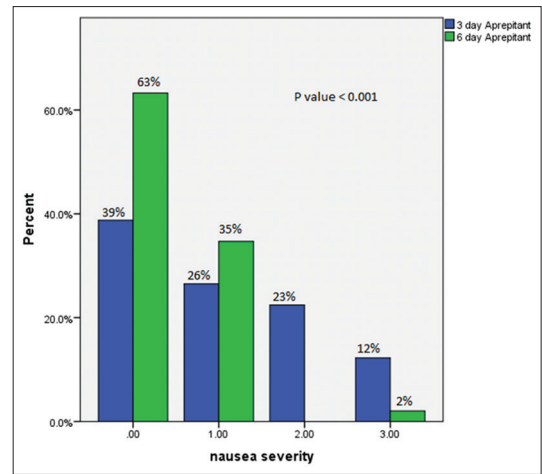


Figure 3: Percentage of patients experiencing different nausea severity (0 = being no nausea, 1 = able to eat reasonable intake, 2 = intake significantly decreased but can eat, 3 = no significant intake)

DISCUSSION

CINV is strong and dreaded the side effect of chemotherapy that can limit the efficacy of cancer treatments and has a potent negative effect on patient quality of life.

Antiemetic therapy should aim to overcome this problem in all cancer patients receiving chemotherapy. Substantial development has been made in improving the control of CINV, largely because of the introduction of antiemetic agents. However, this trend has now been reversed with increasing nausea and vomiting on days 3–5.

This crossover clinical trial in women with breast cancer addressed the potential efficacy of increase in duration of aprepitant consumption from 3 to 6 days for the prevention of nausea and vomiting induced by the combination of AC chemotherapy. The advantage of this crossover clinical trial design is less need for samples, the similarity of a participant in two intervention groups and the least Bayes.

In the current setting, we found that consumption of aprepitant for 6 days was superior to 3 days consumption in the proportion of patients achieving a CR overall after 1-day AC regimen chemotherapy (63% vs. 39%). As seen in previous trials CINV is well controlled on days 1 and 2 with aprepitant regimen. However, loss of control on days 6 through 8 in the delayed phase remains a challenge, therefore adding aprepitant to the standard antiemetic prophylaxis for 6 days provides a significant improvement in complete control for CINV from 43% to 63%.^[22-24] Madsen *et al.* report that a 5-day dosing regimen of aprepitant is highly effective for preventing CINV, although, single doses of oral aprepitant 40 mg or oral aprepitant

125 mg alone were effective for the prevention of postoperative nausea and vomiting.^[25] However, other studies demonstrate 60–80% CR to 3 days administration of aprepitant-containing regimen.^[19,20] Badar *et al.* represent that more than 75% of patients were free from nausea on day 1 and day 2 after use of aprepitant, but This fraction decreased from day 3 to day 7.^[19] This discrepancy may be due to differences in the underlying disease, the patient characteristics, and the chemotherapy regimens the patients received; thus judgments should be made with caution.

We have shown in this study that the number of vomiting episodes is significantly lower during the 6 days aprepitant regimen than during the 3 days regimen. In agreement with our finding, other studies show a significant effect of aprepitant in the episodes of vomiting reduction, in patients treated with HEC regimens.^[26,27]

The main limitation of our study is a lack of placebo group to identify the placebo effect. We cannot allocate placebo group because not to treat nausea and vomiting in a patient who received chemotherapy is unethical.

The present study provides an experimental evidence of increase duration of aprepitant consumption can decline nausea severity. A patient who cannot significant intake due to severe nausea is 12% with 3 days regimen, versus 2% with 6 days regimen. A similar trend was seen in the previous studies where a patient who received 5 days of aprepitant had less nausea on day 6 and day 7.^[28,29]

Hence, we can provide superior prevention of CINV in women with breast cancer only with increasing in the duration of aprepitant consumption.

CONCLUSION

The increase in duration of aprepitant consumption through 6 days resulted in significantly better prevention of CINV than 3 days consumption and provides adequate antiemetic therapy for a patient receiving AC chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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