

A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy

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Abstract *Objectives* This is a single center, randomized, double-blind placebo-controlled study to evaluate the NK(1)-receptor antagonist, aprepitant, in Chinese breast cancer patients. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy. The secondary objective was to compare the patient-reported quality of life in these two groups of patients. *Patients and Methods* Eligible breast cancer patients were chemotherapy-naïve and treated with adjuvant AC chemotherapy (i.e. doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²). Patients were randomly assigned to either an aprepitant-based regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, aprepitant 80 qd) or a control arm which consisted of standard regimen (day 1, ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary, patients quality of life were assessed by self-administered Functional Living Index-Emesis (FLIE).

Results Of 127 patients randomized, 124 were assessable. For CINV in Cycle 1 AC, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea'. The requirement of rescue medication appears to be lesser in patients treated with the aprepitant-based regimen compared to those with the standard regimen (11% vs. 20%; $P = 0.06$). Assessment of FLIE revealed that while there was no difference in the nausea domain and the total score between the two groups; however, patients receiving standard antiemetic regimen had significantly worse quality of life in the vomiting domain (mean score [SD] = 23.99 [30.79]) when compared with those who received the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) ($P = 0.0002$). Both treatments were generally well tolerated. Patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (53.2% vs. 35.5%, $P = 0.0468$), grade ≥ 3 neutropenia (21.0% vs. 45.2, $P = 0.0042$) and delay in subsequent cycle of chemotherapy (8.1% vs. 27.4%, $P = 0.0048$). *Conclusion* The aprepitant regimen appears to reduce the requirement of rescue medication when compared with the control regimen for prevention of CINV in patients receiving both - an anthracycline and cyclophosphamide, and is associated with a better quality of life during adjuvant AC chemotherapy.

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Introduction

Nausea and emesis are major concerns for patients with cancer receiving chemotherapy. Although not life-threatening, these symptoms have been ranked as the two of the

most distressing side effects affecting cancer patients' well-being and overall response to chemotherapy [1, 2]. The development of 5-HT₃ antagonists (granisetron, tropisetron and ondansetron) had been a major step forward in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) [3]. These agents had been widely regarded as the most efficacious anti-emetics available until recently and have been recommended for several years, often in combination with corticosteroids, as the agents of first choice to control nausea and vomiting in most instances [4]. Despite these existing preventative measures, CINV remains a major adverse effect of cancer chemotherapy. These adverse events can have a major impact on patient's quality of life and compliance with treatment, and represent a major therapeutic challenge that potentially threatens the success of therapy.

Aprepitant, a novel neurokinin-1 (NK-1) antagonist, has been recently introduced as a new class of drugs available to prevent CINV. Phase III clinical trials in patients receiving highly emetogenic cisplatin-based chemotherapy as well as in patients receiving moderately emetogenic chemotherapy have shown that aprepitant, in combination with a 5-HT₃ receptor antagonist and dexamethasone, provides superior protection against CINV compared with standard therapy alone when included in preventive regimens [5, 6].

In this study, the objectives were to compare the efficacy of aprepitant-based anti-emetic regimen and standard anti-emetic regimen in Chinese breast cancer patients receiving moderately emetogenic chemotherapy.

Patients and methods

This is a single center, randomized, double-blind, placebo-controlled study. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of CINV in Chinese breast cancer patients receiving the first cycle of moderately emetogenic chemotherapy AC (doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m²). The secondary objective was to compare the patient-reported quality of life in these two groups of patients. The study was approved by the Joint CUHK-NTEC Institution Review Board of the Chinese University of Hong Kong.

Patients were eligible if they were ethnic Chinese female age over 18 years diagnosed with breast cancer, were scheduled to receive their first course of adjuvant chemotherapy that consisted of intravenous doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m². Other eligibility criteria included predicted life expectancy of ≥ 4 months, Karnofsky score ≥ 60 , negative for pregnancy test and having agreed to use a double-barrier method of

contraception prior to, throughout, and for at least 14 days following the last dose of study medication (for premenopausal patients), being able to read, understand and complete study questionnaires and diary, including questions requiring a visual analog scale response; as well as understanding the procedures and having agreed to participate in the study by giving written informed consent.

Patients were excluded from the study if they had abnormal laboratory results including absolute neutrophil count $< 1500/\text{mm}^3$, white cell count $< 3000/\text{mm}^3$, platelet count $< 100,000/\text{mm}^3$, aspartate transaminase or alanine transaminase $> 2.5 \times$ upper limit of normal, bilirubin $> 1.5 \times$ upper limit of normal, or serum creatinine $> 1.5 \times$ upper limit of normal. Patients were also excluded if they had received or would receive radiation therapy to the abdomen or pelvis in the week prior to study treatment, had vomited in the 24 h prior to study treatment, had a history of treatment with emetogenic chemotherapy (Hesketh Level 3 or above), had an active infection or any uncontrolled disease, had alcohol abuse or use of any illicit drugs, were mentally incapacitated or has a significant emotional or psychiatric disorder, or had a history of hypersensitivity to ondansetron or dexamethasone.

Patients were assigned to 1 of 2 anti-emetic regimens according to an in-house blinding and allocation schedule of random numbers. The aprepitant-based antiemetic regimen consisted of aprepitant 125 mg, ondansetron 8 mg, dexamethasone 12 mg, before chemotherapy and ondansetron 8 mg 8 h later on day 1; aprepitant 80 qd on days 2–3. The control arm of standard anti-emetic regimen consisted of ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and ondansetron 8 mg 8 h later on day 1; ondansetron 8 mg bid on days 2–3. Patients in both study groups were given the same number of tablets to be taken, which consisted of aprepitant, ondansetron, dexamethasone and placebo. Patients were instructed to take rescue therapy (metoclopramide 20 mg every 6 h as required) if needed for nausea or vomiting.

Each patient kept a diary to monitor the anti-emetic efficacy for 120 h following the chemotherapy infusion. The diary documented vomiting episodes, use of rescue therapy, and daily nausea ratings (by visual analogue scale VAS; 0 mm implied no nausea; 100 mm implied nausea that was "as bad as it could be"). Patients recorded the date and time of any emetic episode(s) and use of rescue medication. On days 2–6, they were asked to record the nausea rating for the preceding 24 h using the VAS. After patients have completed the diary on the morning of day 6, they would immediately complete the Functional Living Index-Emesis (FLIE) questionnaire. The nurse coordinator would call individual patient each morning on days 2–6, in order to assist them in the proper completion of the patient diary, to remind them to take the study medications as

directed, and to remind them to complete the FLIE questionnaire.

Assessments of efficacy began at the initiation of chemotherapy infusion (0 h) until the morning of day 6 (~120 h) after chemotherapy in the first cycle of AC. Post-initiation of AC, 0–24 and 24–120 h were defined as “acute” and “delayed” time frames, respectively, while 0–120 h was defined as “overall” time frame.

For the purposes of this study, the primary variable used to evaluate anti-emetic efficacy was the proportion of patients reporting “Complete Response” (defined as no vomiting and no use of rescue therapy) during the overall time frame. Other variables that were assessed in the “overall,” “acute” and “delayed” time frames included: the proportion of patients with “No Vomiting” (no vomiting or retching including patients who received rescue therapy), “No Significant Nausea” (nausea VAS <25 mm), “No Nausea” (nausea VAS < 5 mm), “No use of Rescue Therapy”, “Complete Protection” (no vomiting with no rescue therapy and nausea VAS < 25 mm) and “Total Control” (no vomiting with no rescue therapy and nausea VAS < 5 mm).

Quality of life assessment was conducted using patient-reported FLIE questionnaire Chinese version. The FLIE questionnaire is a validated instrument for measurement of impact on daily living associated with CINV [7]. It is a short, self-administered instrument containing the nausea domain (9 items) and the vomiting domain (9 items). The questionnaire was administered before the initiation of chemotherapy infusion on day 1, and on day 6, immediately after completion of the diary, which would cover the overall time frame. Responses to each question were rated on a 100-mm VAS that was scored on a 1- to 7-point scale. For most items, the larger the score the worse the effect was on the patients’ quality of life; for other items, the reverse holds and these scores would be transferred back to having similar direction as the majority of the items.

Finally, data on the timing (date and time) of each vomiting episode was recorded by the patient in the Cycle 1 diary at the time of occurrence and “the time to first vomiting episode” was evaluated. Adverse experiences were graded according to NCI Common Toxicity Criteria.

Patients were continually monitored to ensure that they took study medication as required per protocol. The number of tablets and capsules taken on each day was used to assess the treatment compliance. Patients who did not comply with the protocol were excluded from the per-protocol analyses.

Statistical analysis

To address the primary objective, the aprepitant-based regimen was compared to the standard regimen with respect to the proportion of patients reporting Complete

Response from 0 to 120 h following initiation of the first cycle of moderately emetogenic AC chemotherapy.

Based on the average nausea scores as measured using VAS, the standard deviation is around 19–20 and a 10 mm difference is generally considered clinically important. Assuming the response rate with control regimen is 40%, this study would have 80% power to detect 25% difference with two-sided alpha level at 0.05, the number of patient per groups is 61 and the total number of patient to be recruited is 122.

Eighty patients (approximately 40 patients per treatment group) were enrolled and the data was incorporated to that of 44 patients (approximately 22 in each arm) who took part in the earlier multi-centre study [6]. Thus, data from 124 evaluable patients (62 in each arm) was available for analysis.

The modified intention-to-treat (mITT) approach was used for all efficacy analyses. Only patients who had received chemotherapy, taken all the doses of the study drugs and had at least one post-treatment assessment were included in the analysis.

The primary efficacy analysis compared the aprepitant-based regimen to the standard regimen with respect to the proportion of patients reporting Complete Response 0–120 h following initiation of MEC in the first cycle of chemotherapy. All other efficacy endpoints were compared using the Chi-square test with a two-sided significance level of 5%.

The time to first vomiting (time to failure) was compared between the two treatment groups using the Log-Rank test.

For the analysis of the FLIE questionnaire, the nausea domain, vomiting domain and the total score (the sum of the two domains) in the “overall” time frame was compared between the two groups using the Wilcoxon Rank Sum Test.

The incidences of serious adverse events (SAEs) and specific adverse events (AEs) occurring in $\geq 3\%$ of patients were summarized by treatment group. The comparison between the treatment groups were performed by using chi-square test for specific AEs occurring in $\geq 3\%$ of patients.

Results

Of 127 patients randomized, 124 were assessable. All patients were of ethnic Chinese origin. Three patients were excluded from the analysis: two receiving the aprepitant-based regimen arm and one receiving the standard regimen did not take the study medication on day 2. The compliance of 124 patients was 100%; thus, they were included in the efficacy analysis (62 in the aprepitant-based regimen and 62 in the standard regimen).

Patient characteristics are listed in Table 1. For patients in the aprepitant-based regimen and the standard regimen respectively, the median age were 46.5 and 48.5 years, 77% and 81% had history of motion sickness, 36% and 27% had history of vomiting during pregnancy, 95% and 94% had invasive ductal carcinoma, 45% and 55% had stage II breast cancer.

The outcomes of emesis control are listed in Tables 2 and 3. In the overall time frame (0–120 h) in cycle 1 of AC chemotherapy, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, “no vomiting”, “no significant nausea” and “no nausea”. The requirement of rescue medication appears to be lesser in the aprepitant group than the control group (11% vs. 20%; $P = 0.06$) (Table 2). There was also no significant difference between the two groups with respect to all the parameters of emesis control in the acute and delayed time frames (Table 3).

The median time to first vomiting after the initiation of chemotherapy was 64.4 h for the aprepitant arm and 52.6 h in the control arm ($P = 0.78$).

When the impact on daily living was assessed using the FLIE questionnaire, while there was no difference in the nausea domain and the total score between the two groups, patients on the standard regimen had a significantly worse quality of life in the vomiting domain assessment (mean score [SD] = 23.99 [30.80]) when compared with those on

Table 1 Baseline characteristics of breast cancer patients in the study

	Aprepitant-based n (%)	Standard n (%)
Patient number	62	62
Median age (range)	46.5 (32–66)	48.5 (26–68)
History of motion sickness		
No	48 (77.4)	50 (80.6)
Yes	14 (22.6)	12 (19.4)
History of vomiting during pregnancy		
Yes	22 (35.5)	17 (27.4)
No	28 (45.2)	32 (51.6)
Never been pregnant	12 (19.3)	13 (21.0)
Primary histology		
Invasive ductal carcinoma	59 (95.2)	58 (93.5)
Invasive lobular carcinoma	1 (1.6)	0 (0)
Other	2 (3.2)	4 (6.5)
Stage of disease		
I	18 (29.0)	9 (14.5)
II	28 (45.2)	34 (54.8)
IIIa	13 (21.0)	10 (16.1)
IIIb	3 (4.8)	9 (14.5)

Table 2 Emesis endpoints in the overall time frame (0–120 h)

	Aprepitant-based (%)	Standard (%)	<i>P</i> -value
No vomiting	54.8	50.0	0.58
No rescue	82.3	67.7	0.06
No significant nausea	66.1	62.9	0.71
No nausea	30.6	35.5	0.57
Complete response	46.8	41.9	0.58
Complete protection	38.7	41.9	0.71
Total control	25.8	30.6	0.55

the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) ($P = 0.0002$) (Table 4).

Both treatment arms were generally well tolerated. Amongst the AEs, when compared with the standard regimen, patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (35.5% vs. 53.2%, $P = 0.0468$), grade ≥ 3 neutropenia (21.0% vs. 45.2%, $P = 0.0042$) and delay in subsequent cycle of chemotherapy (8.1% vs. 27%, $P = 0.0048$). In addition, the incidence of constipation in the standard arm was twice as much as that in the aprepitant-based arm (11.3% vs. 5.6%, $P = 0.09$). There was no significant difference in other adverse events between the two groups of patients (Tables 5, 6).

Discussion

The incidence of CINV depends on multiple factors, including the chemotherapy regimen, and is frequently underestimated by care givers [8]. The NK-1 antagonist aprepitant is a potent new anti-emetic which has demonstrated clear superiority over existing anti-emetic modalities [5, 6]. Until recently, 5-HT₃ serotonin antagonists, usually combined with corticosteroids, were considered the standard of care in patients treated with highly and moderately emetogenic chemotherapy [9]. The 2006 updated American Society of Clinical Oncology guidelines [10] for the use of anti-emetics in oncology recommend the aprepitant-based regimen in patients receiving highly emetogenic chemotherapy (HEC) as well as in patients receiving MEC like anthracycline and cyclophosphamide. Further, CINV has economical consequences as it leads to the use of rescue medications and to additional outpatient hospital and office physician visits and even hospital admissions [11]. Cost-effective analysis has reported that the implementation of the aprepitant-based regimen would result in cost savings in both HEC and MEC regimens compared to the standard preventive anti-emetic treatment [12].

Table 3 Emesis endpoints in the acute (0–24 h) and delay time frames (24–120 h)

	Acute (0–24 h)			Delay (24–120 h)		
	Aprepitant-based	Standard	<i>P</i> -value	Aprepitant-based	Standard	<i>P</i> -value
No vomiting	72.1	74.2	0.79	75.6	67.4	0.39
No rescue	98.4	95.2	0.31	83.6	71.2	0.10
No significant nausea	88.5	83.9	0.45	74.1	75.0	0.91
No nausea	62.3	59.7	0.76	47.3	59.5	0.29
Complete response	72.1	72.6	0.95	64.4	57.8	0.51
Complete protection	67.2	72.6	0.51	56.1	57.8	0.87
Total control	54.1	56.5	0.79	45.5	54.3	0.47

Table 4 Patients' scoring for Functional Living Index Emesis questionnaire

	Aprepitant-based		Standard		<i>P</i> -value
	Mean score	SD	Mean score	SD	
Nausea domain	26.74	25.51	31.75	31.95	0.84
Vomiting domain	3.40	13.18	23.99	30.80	0.0002
Total score	11.24	15.66	23.12	30.49	0.45

Table 5 Incidences of adverse events that occurred in $\geq 3\%$ of patients in the aprepitant-based regimen and the standard regimen

	Aprepitant-based regimen (%)	Standard regimen (%)	<i>P</i> -value
Alopecia	85.5	79.0	0.3471
Insomnia	6.5	8.1	0.7292
Dizziness	6.5	3.2	0.4026
Fatigue	25.8	21.0	0.5245
Anorexia	16.1	21.0	0.4882
Constipation	11.3	22.6	0.0937
Diarrhoea	16.3	9.7	0.2839
Oral mucositis	29.0	38.7	0.2549
Heartburn	4.8	4.8	1.0000
Nausea	11.3	11.3	1.0000
Vomiting	3.2	4.8	0.6480
Febrile neutropenia	4.8	8.1	0.4647
Fever	4.8	4.8	1.0000
Neutropenia	35.5	53.2	0.0468
Rigors/chills	3.2	3.2	1.0000
Cough	6.5	9.6	0.5095
Dermatology/skin other	3.2	9.6	0.1437
Headache	3.2	4.8	0.6480
Pain-Throat/pharynx/larynx	9.6	9.6	1.0000

This is the first study of aprepitant in a homogenous group of Chinese breast cancer patient receiving a uniform protocol of adjuvant AC chemotherapy. In the present study, there was no significant difference observed in the

control of CINV using aprepitant-based anti-emetic regimen when compared with standard anti-emetic regimen in Chinese breast cancer patients undergoing moderately emetogenic adjuvant chemotherapy. This may be due to the incorporation of active therapy with ondansetron for 3 days in the standard regimen. Further, when the outcomes of the aprepitant-based treated patients were compared with those treated with the standard regimen, the latter group had a relatively higher proportion of patients taking rescue medication (18% vs. 32%), which has led to a similar proportion of patients achieving “no vomiting” after chemotherapy. As “no rescue medication” and “no vomiting” were two components of “complete response”, it could partly explain the equivocal rate of complete response in the two groups of patients.

On the other hand, when compared with a large international anti-emetic study which consisted of breast cancer patients mainly from the West [6], there appears to be ethnic differences in the willingness to take medications, with less Chinese patients taking rescue medication (18% vs. 41% in the aprepitant-based arms, and 32% vs. 44% in the standard arms). Chinese are reluctant to take medications whenever these are considered to be ‘not absolutely necessary’. As a consequence, the proportion of patients achieving ‘no vomiting’ status after chemotherapy was lower in the present study when compared with the international study (55% vs. 76% in the aprepitant-based arms, and 50% vs. 59% in the standard arms). Another potentially locally relevant factor is the anecdotal observation of a tendency amongst some Chinese patients to self-administer Traditional Chinese Medicine (TCM) during cytotoxic therapy. TCM is considered by some Chinese to possess anti-cancer activity as well as to ameliorate chemotherapy-related toxicity. In the present study, patients were asked not to take TCM prior to study entry; none-the-less, prospective data on practice of TCM was collected from the latter 80 patients of the study, which revealed that <1% of the studied subjects had taken TCM at any time during the study period.

Apart from potential inter-ethnic behavioural differences, genetic variation in drug metabolism of aprepitant

Table 6 Incidences of serious adverse events, neutropenic fever, chemotherapy dose delay and dose reduction in the aprepitant-based regimen and the standard regimen

	Aprepitant-based (%)	Standard (%)	P-value
Dose reduction for subsequent AC	0	0	–
Delay in subsequent AC	8.1	27.4	0.0048
Neutropenic fever	4.8	8.1	0.4647
Serious adverse events			
Dizziness	1.6	0	0.3192
Rash	1.6	0	0.3192
Neutropenia	21.0	45.2	0.0042

could not be excluded. Aprepitant is both a substrate and a moderate inhibitor of CYP3A4 [13]. The genetic diversity in drug metabolism that involve complex regulatory pathways may confound evaluation of the effect of individual CYP3A genetic variations on drug disposition, efficacy and safety [14, 15].

Nausea and vomiting are frequently associated with cytotoxic chemotherapy and have been shown to have a profound negative effect on health-related quality of life [1]. Although the efficacy of aprepitant-based anti-emetic regimen was similar to standard regimens, the present study has revealed that use of aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting, while there was no difference in the nausea domain. This confirms that the agent is active against vomiting induced by serotonin and substance P, while nausea is possibly related to some other neurotransmitters for which aprepitant has limited efficacy.

As seen in previous studies, the aprepitant regimen was well tolerated [16, 17]. Earlier studies assessing aprepitant use [6, 16, 17] showed a trend toward more fatigue but less constipation with the aprepitant regimen. A similar observation was found in the present study with increased constipation in the standard regimen, which contained multiple days of 5-HT3 antagonist that has been shown to be associated with this symptom. Of interest, the other notable difference between the treatment groups were lesser incidence of delay in subsequent chemotherapy in the patients treated with the aprepitant-based regimen, which was possibly related to the reduced incidence of neutropenia and grade ≥ 3 neutropenia.

In conclusion, the addition of aprepitant to ondansetron and dexamethasone resulted in significantly better quality of life than the latter two agents alone in patients receiving moderately emetogenic chemotherapy. However, current data suggested that the new anti-emetic regimens did not have definitive superiority over existing regimens in Chinese patients; with only half of the patients achieving

complete response and 30% of patients achieving total control for CINV. Further studies are warranted to assess ways to enhance the aprepitant-based regimen, which may involve a prolonged administration of ondansetron and dexamethasone that could potentially improve emetic control in this patient population.

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