



<b>Title</b>	<b>Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer After Moderately Emetogenic Chemotherapy</b>
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## Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer After Moderately Emetogenic Chemotherapy

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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### A B S T R A C T

#### Purpose

This is the first study in which the NK<sub>1</sub>-receptor antagonist, aprepitant (APR), was evaluated for the prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately emetogenic chemotherapy.

#### Patients and Methods

Eligible breast cancer patients were naive to emetogenic chemotherapy and treated with cyclophosphamide ± doxorubicin or epirubicin. Patients were randomly assigned to either an aprepitant regimen (day 1, APR 125 mg, ondansetron (OND) 8 mg, and dexamethasone 12 mg before chemotherapy and OND 8 mg 8 hours later; days 2 through 3, APR 80 qd) or a control regimen (day 1, OND 8 mg and dexamethasone 20 mg before chemotherapy and OND 8 mg 8 hours later; days 2 through 3, OND 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary. The primary efficacy end point was the proportion of patients with complete response, defined as no vomiting and no use of rescue therapy, during 120 hours after initiation of chemotherapy in cycle 1. The secondary end point was the proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index–Emesis questionnaire.

#### Results

Of 866 patients randomized, 857 patients (99%) were assessable. Overall complete response was greater with the aprepitant regimen than with the control regimen (50.8% v 42.5%; *P* = .015). More patients in the aprepitant group reported minimal or no impact of CINV on daily life (63.5% v 55.6%; *P* = .019). Both treatments were generally well tolerated.

#### Conclusion

The aprepitant regimen was more effective than the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide.

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### INTRODUCTION

Despite the use of a 5-HT<sub>3</sub>-receptor antagonist and dexamethasone in accordance with evidence-based consensus guidelines, many cancer patients still experience chemotherapy-induced nausea and vomiting (CINV). Although cisplatin is recog-

nized as being particularly emetogenic, numerous other chemotherapeutic agents are also emetogenic, particularly when administered in combination regimens. A variety of classification schemes defining emetogenicity of individual chemotherapeutic agents have been published in which a cisplatin dose of more than 50 mg/m<sup>2</sup> is

consistently defined as being highly emetogenic, and agents such as cyclophosphamide, doxorubicin, and epirubicin are generally defined as being moderately emetogenic.<sup>1,2</sup>

Recommended antiemetic therapy for moderately emetogenic chemotherapy (MEC) consists of a corticosteroid plus a 5-HT<sub>3</sub>-receptor antagonist before chemotherapy, followed by a 5-HT<sub>3</sub>-receptor antagonist and/or a corticosteroid on subsequent days.<sup>2,3</sup> Many physicians are reluctant to prescribe corticosteroids on multiple days, and so the most common approach is to use a 5-HT<sub>3</sub>-receptor antagonist on multiple days.<sup>4</sup> It is notable that recent studies describe an incidence of CINV of approximately 50% in patients receiving MEC,<sup>5-8</sup> including breast cancer patients treated with 5-HT<sub>3</sub>-receptor antagonists.<sup>9,10</sup> Hence, there is clearly a need for more effective prevention of CINV in patients receiving MEC, especially in women, who are particularly susceptible to these symptoms.<sup>11</sup>

Several lines of evidence suggest that NK<sub>1</sub>-receptor antagonists, such as aprepitant, might be useful antiemetics in the prevention of CINV associated with emetogenic noncisplatin-based chemotherapy and other regimens defined as moderately emetogenic chemotherapy. Several large studies have shown that addition of aprepitant to a regimen including granisetron or ondansetron and dexamethasone improved the prevention of emesis throughout the acute and delayed phases in patients receiving cisplatin-based highly emetogenic chemotherapy (HEC).<sup>12-14</sup> The benefit of aprepitant appeared to be particularly pronounced in patients receiving cisplatin with cyclophosphamide and/or doxorubicin.<sup>15</sup> Antiemetic therapies that have been shown to be effective in preventing CINV associated with cisplatin, such as 5-HT<sub>3</sub>-receptor antagonists, dopamine-receptor antagonists, and corticosteroids, have consistently also been shown to be effective in preventing CINV associated with other chemotherapy agents. Finally, preclinical studies had previously shown that another NK<sub>1</sub>-receptor antagonist, GR203040, prevented emesis in ferrets treated with cyclophosphamide.<sup>16</sup>

This study of aprepitant in breast cancer patients treated with cyclophosphamide-based chemotherapy was designed to clarify the potential role of an NK<sub>1</sub>-receptor antagonist in patients receiving MEC. The study compared the efficacy and tolerability of an aprepitant regimen with an active control regimen in preventing CINV in a patient population that is known to be very susceptible to CINV. The primary hypothesis was that the aprepitant regimen would be superior to the control regimen, as measured by the proportion of patients with complete response, which was defined as no vomiting and no rescue therapy, throughout the acute and delayed phases (120 hours) after the first cycle of chemotherapy, and that both regimens would be well tolerated. The secondary hypothesis was that the aprepitant regimen would be superior to the control regimen in the proportion of patients with minimal or no

impact of emesis on daily living, as measured using the Functional Living Index–Emesis (FLIE) questionnaire.

## PATIENTS AND METHODS

### Inclusion Criteria

Patients were included in the study if they had breast cancer that was being treated with moderately emetogenic chemotherapy that included intravenous cyclophosphamide. Institutional review boards at each study site approved the study protocol, and written informed consent was obtained from all participants before enrollment. Patients were at least 18 years old and had to be naive to emetogenic chemotherapy (Hesketh Level 3 or higher<sup>1</sup>), and scheduled to receive their first course of MEC. The following agents were administered either alone or in combination: intravenous (IV) cyclophosphamide 750 to 1,500 mg/m<sup>2</sup> ( $\pm$  5%); IV cyclophosphamide 500 to 1,500 mg/m<sup>2</sup> ( $\pm$  5%) and IV doxorubicin  $\leq$  60 mg/m<sup>2</sup> ( $\pm$  5%); IV cyclophosphamide 500 to 1,500 mg/m<sup>2</sup> ( $\pm$  5%) and IV epirubicin  $\leq$  100 mg/m<sup>2</sup> ( $\pm$  5%); other chemotherapeutic agents Hesketh Level 2 or lower were allowed to be added to the above chemotherapeutic regimens. Patients had to have a predicted life expectancy of  $\geq$  4 months and a Karnofsky score of  $\geq$  60 to be eligible for the study.

### Exclusion Criteria

Patients were excluded if they had a symptomatic CNS malignancy; received radiation therapy to the abdomen or pelvis in the week before treatment; had vomited in the 24 hours before treatment day 1; had an active infection, an active systemic fungal infection, or any severe concurrent illness except for malignancy; or had abnormal laboratory values (including absolute neutrophil count  $<$  1,500/mm<sup>3</sup>, WBC count  $<$  3,000/mm<sup>3</sup>, platelet count  $<$  100,000/mm<sup>3</sup>, AST  $>$  2.5 $\times$  the upper limit of normal, ALT  $>$  2.5 $\times$  the upper limit of normal, bilirubin  $>$  1.5 $\times$  the upper limit of normal, creatinine  $>$  1.5 $\times$  the upper limit of normal). Patients taking systemic corticosteroid therapy at any dose were excluded. Antiemetic agents could not be administered within 48 hours before treatment, except for single daily doses of lorazepam.

### Study Design

This was a prospective, double-blind, double-dummy, parallel-group study conducted at 95 centers in the United States, Germany, Austria, Canada, Hong Kong, Hungary, Spain, United Kingdom, Italy, Australia, and Greece. Patients in each treatment group were instructed to take a daily dose of the study drug for the 3-day period, according to the treatment regimens listed in Table 1. The value of 5-HT<sub>3</sub>-receptor antagonists during the acute phase is well recognized, so ondansetron was included in both treatment groups on day 1. Because the value of 5-HT<sub>3</sub>-receptor antagonists in the delayed phase is of uncertain benefit, the most parsimonious approach was taken when deciding treatment during this period, which was to eliminate the ondansetron and replace it with aprepitant. To ensure similar dexamethasone plasma exposure between treatment groups, the dexamethasone dose in the aprepitant regimen was reduced by 40%, based on a pharmacokinetic study that showed that aprepitant increased dexamethasone levels by approximately two-fold.<sup>17</sup> On days 4 and 5, measurements were taken, but no treatment was given. Patients kept a diary to monitor efficacy from the initiation of chemotherapy infusion (0 hours) until the morning of day 6 ( $\approx$  120 hours) after chemotherapy infusion. The diary documented the date and time of any emetic

**Table 1.** Study Medication Schedule

Regimen and Study Medication	Dose		
	Day 1	Day 2	Day 3
<b>Aprepitant (n = 438)</b>			
Aprepitant	125 mg po 1 hour before chemotherapy	80 mg po	80 mg po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	Placebo po bid	Placebo po bid
Dexamethasone	12 mg po 30 minutes before chemotherapy		
<b>Control (n = 428)</b>			
Aprepitant	Placebo po	Placebo po	Placebo po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	8 mg po bid	8 mg po bid
Dexamethasone	20 mg po 30 minutes before chemotherapy		

Abbreviation: po, orally.

episodes and use of rescue medication, as well as daily nausea ratings (by visual analog scale [VAS]; 0 mm is “no nausea,” 100 mm is “nausea as bad as it could be.”) Patients were allowed to take rescue therapy throughout the study for nausea or vomiting as needed; permitted rescue medications were: 5-HT<sub>3</sub>-antagonists, phenothiazines, butyrophenones, benzodiazepines, benzamides, corticosteroids, and domperidone. The results presented here are for cycle 1 only; results for additional cycles will be the subject of a future article. Note that the data for cycle 1 was not unblinded for analysis until all patients randomly assigned to the study had completed the study.

### Patient-Reported Impact on Daily Life

The FLIE questionnaire is a validated patient-reported measure of the impact of CINV on daily life.<sup>18</sup> It is a short, self-administered instrument containing two domains—one for nausea (9 items) and one for vomiting (9 items). The FLIE questionnaire was administered before the initiation of chemotherapy infusion on day 1, and on day 6, immediately after completion of the diary. Responses to each question are rated on a 100-mm VAS that was scored on a 1- to 7-point scale as described in the FLIE Scoring Manual. For this study, “minimal or no impact of CINV on daily life” is defined as an average score of more than 6 on the 7-point scale (ie, > 108 total score [nausea domain score + vomiting domain score] or > 54 domain score).

### Statistical Methods

Patients who met eligibility criteria were randomly assigned to either the aprepitant regimen or the control regimen using a computer-generated allocation schedule with a block size of four. With a sample size of 375 assessable patients per regimen, and assuming a response rate with the control regimen of 52% (data on file, Merck & Co Inc pilot study), this study would have approximately 80% power to detect the superiority of the aprepitant regimen, if the true aprepitant regimen effect is 10 percentage points higher than the control regimen. A type I error of 0.05 was used in the determination of sample size.

Surveillance of the emerging study data was carried out by an independent group, the Data Safety and Monitoring Board (DSMB). The DSMB were unblinded to study safety data as deemed necessary to fulfill its charge of identifying safety issues and assessing (and identifying) drug-related treatment-emergent adverse events (AE) in order to make periodic recommendations

on protocol modifications, and on whether to continue or terminate the study.

The primary efficacy hypothesis was that the aprepitant regimen would be superior to the control regimen in the proportion of patients with complete response, which was defined as no vomiting with no use of rescue therapy, in the 120 hours after the first cycle of chemotherapy. The primary safety hypothesis was that the aprepitant regimen and the control regimen would be well tolerated in the first cycle of chemotherapy. The secondary hypothesis stated that the aprepitant regimen would be superior to the control regimen in the proportion of patients with minimal or no impact on daily life according to the FLIE questionnaire during the first cycle of chemotherapy.

A modified intention-to-treat (mITT) approach was used for all efficacy analyses; a patient must have received chemotherapy, been administered a dose of the study drug, and have at least one post-treatment assessment on day 1 (required for acute phase) and day 2 (required for both delayed phase and overall analyses) to be included in the analysis. However, if a patient's treatment was identified as a “failure” in the overall or delayed phases, regardless of the day in the phase, then that patient was included in the mITT analysis for that respective phase in cycle 1. The primary end point used to evaluate efficacy was the proportion of patients reporting complete response during the overall 0 to 120 hours after initiation of MEC (cycle 1). Exploratory end points included complete response in the acute and delayed time frames (0 to 24 and 24 to 120 hours, respectively), and the following in acute, delayed, and overall time frames: no emesis (no vomiting or retching), no use of rescue therapy, no significant nausea (VAS < 25 mm), and no nausea (VAS < 5 mm). The time to first vomiting episode was also assessed. For all binary outcome efficacy measures, comparison between the aprepitant regimen and the control regimen was made using a logistic regression model with factors for treatment allocation, investigator group (grouped by region in the United States, East versus Middle/West, and by country for non-US groups, to avoid sparse data problems), and age category (< 55 years, ≥ 55 years). All tests of hypothesis used a two-sided significance level of 5%. Interactions between treatment and investigator group, and treatment and age category (< 55 years, ≥ 55 years) were assessed in a separate model using a significance level of .10. For the time to first vomiting episode, Kaplan-Meier curves depicting the percentage of patients who had no vomiting

episodes since the initiation of chemotherapy were generated for each of the treatment regimens. A log-rank test stratifying investigator group and age category (< 55 years, ≥ 55 years) was used for the treatment comparison.

For the analysis of the FLIE questionnaire, treatment groups were compared with respect to the proportion of patients with a total score of more than 108 (minimal or no impact) using a logistic regression model. If the proportion of patients with minimal or no impact was statistically significantly different between groups, then a separate evaluation would be carried out for each domain (nausea, vomiting) score, and, if significant for a domain, for

three individual items for each domain (ability to enjoy a meal, daily functioning, and personal hardship). Hochberg's procedure was used as a multiplicity adjustment when testing individual items.<sup>19</sup>

All patients treated were included in the safety analyses. Safety and tolerability were assessed by statistical and clinical review of AEs, vital signs, and laboratory values. The primary variable for the safety assessment was the incidence of overall AEs occurring in cycle 1. Fisher's exact test was used to make treatment comparisons with respect to the incidence of AEs.

The statistical analyses were completed by the study sponsor with significant input from the study investigators.

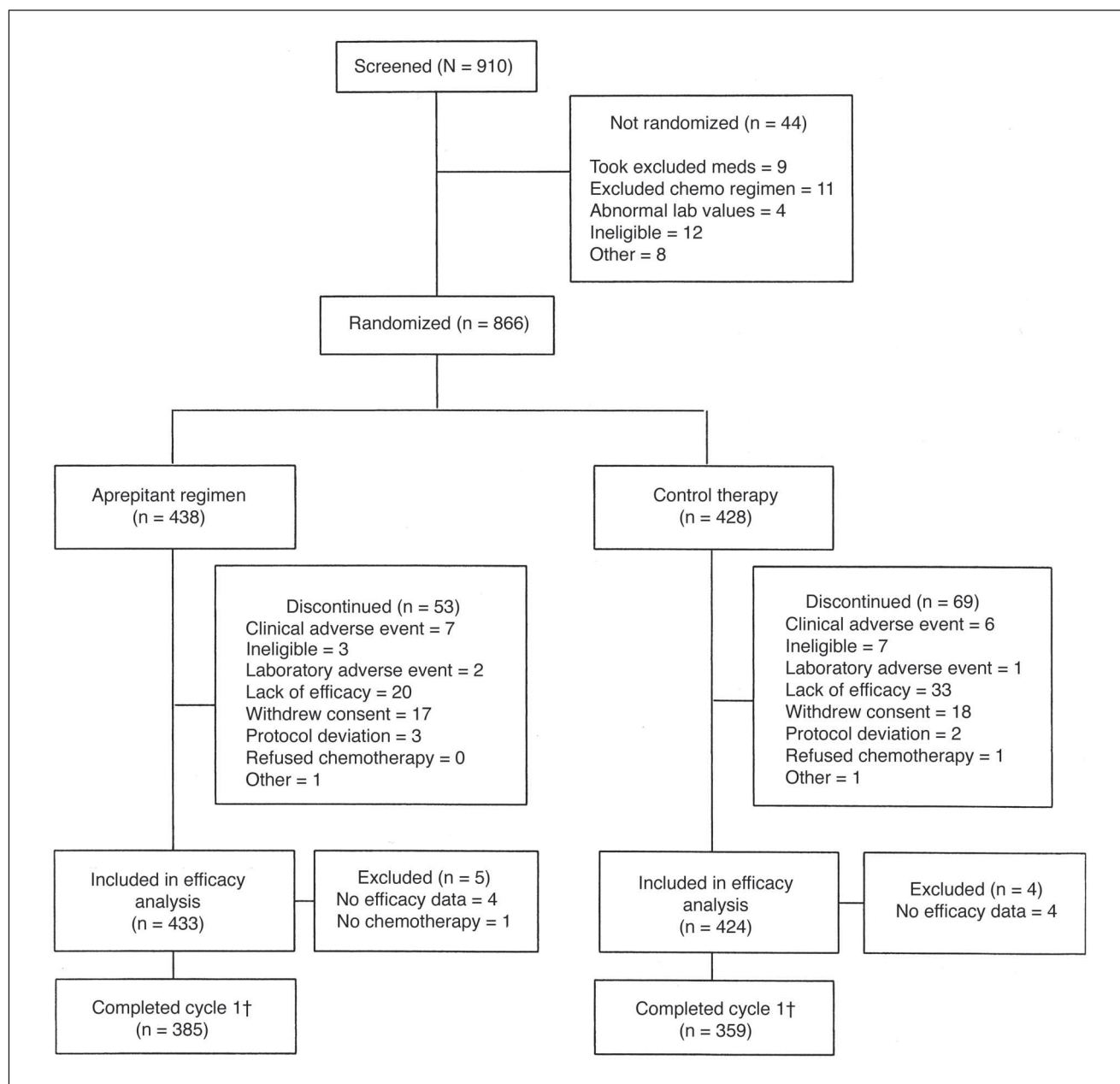


Fig 1. Study flow chart. Patient disposition during the study. (†) Completed the day 14 to 29 visit. Chemo, chemotherapy.

## RESULTS

From October 2002 to December 2003, 866 patients from 95 centers around the world were randomly assigned to either the aprepitant regimen or the control regimen. Patient accounting is shown in Figure 1. A fairly small percentage (5%) of potentially eligible patients did not enroll onto the study. Nine patients (1%) were considered ineligible for evaluation and were excluded from the modified intention-to-treat analysis of the primary end point.

Patient characteristics and treatment regimens are listed in Table 2. Treatment groups were similar with respect to baseline characteristics. The majority of patients were white (78.6%) and female (99.8%). Ninety-nine percent of patients received a combination of cyclophosphamide plus an anthracycline as their chemotherapy regimen; six patients received cyclophosphamide plus fluorouracil plus methotrexate.

### Complete Response

The primary efficacy end point of overall complete response is defined as no emetic episodes and no use of rescue medication during the 5 days (120 hours) after initiation of chemotherapy. Overall, significantly more patients in the aprepitant group reported complete response than in the control group (51% v 42%;  $P = .015$ , adjusted for

treatment group, investigator group, and age category; Fig 2). A sensitivity analysis was performed adjusting only for treatment group, and showed similar results with  $P = .014$ . There was no evidence of treatment-by-subgroup interactions, including race. More patients taking aprepitant achieved a complete response during both acute (76% v 69%;  $P = .034$ ) and delayed (55% v 49%;  $P = .064$ ) phases (Fig 3). Analysis of the components of complete response, vomiting and using rescue medication, showed that significantly more patients taking aprepitant reported no vomiting (76% v 59%;  $P < .001$ ), but there was no significant difference between groups in the use of rescue therapy.

### Impact on Daily Living

On the FLIE questionnaire, significantly more patients taking the aprepitant regimen reported minimal or no impact on daily living overall (Fig 4). There were significant differences favoring aprepitant in the vomiting domain score (85.7% v 71.8%;  $P < .001$ ), as well as in individual items, but not in the nausea domain score (53.5% v 50.5%).

### Exploratory End Points

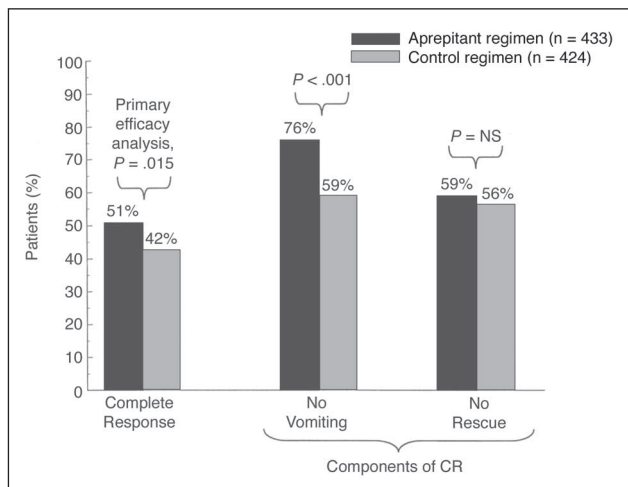
Figure 5 shows the Kaplan-Meier curve for the time to first emesis after the initiation of chemotherapy. The superiority of the aprepitant regimen versus the control regimen

**Table 2.** Patient Characteristics

Characteristics	% of Patients	
	Aprepitant Regimen (n = 438)	Control Regimen (n = 428)
Female	99.5*	100
Age, years		
Mean	53.1	52.1
SD	10.7	10.9
Race, white	79.7	77.6
History of motion sickness	16.9	21.0
History of vomiting during pregnancy	30.8	30.1
Primary diagnosis		
Infiltrating ductal carcinoma	81.5	83.2
Infiltrating lobular carcinoma	8.7	7.0
Stage of malignancy		
I	21.5	22.2
II	57.5	57.9
IIIa	11.6	11.0
IIIb	5.5	4.7
IV	3.4	3.3
Chemotherapy regimen		
Cyclophosphamide + doxorubicin	61.0	60.3
Cyclophosphamide + doxorubicin + docetaxel	0.5	0.9
Cyclophosphamide + doxorubicin + fluorouracil	7.8	7.0
Cyclophosphamide + doxorubicin + paclitaxel	0.5	0
Cyclophosphamide + epirubicin	8.0	8.4
Cyclophosphamide + epirubicin + fluorouracil	20.8	22.4
Cyclophosphamide + fluorouracil + methotrexate	1.4	0.9

Abbreviation: SD, standard deviation.

\*Two patients were men.



**Fig 2.** Complete response (CR) and components. Bar graph showing the percentage of patients with a CR, defined as no vomiting and no use of rescue therapy, during the 120 hours after the initiation of the first cycle of chemotherapy. *P* values are for between-group differences. Black bars = aprepitant regimen; gray bars = control regimen. NS, not significant.

became apparent early, at approximately 6 hours, and the gap between the treatments continued to widen over the 5-day period. There were no significant differences between the two treatment groups in reports of overall nausea (VAS < 5 mm; 33% for both) or significant nausea (VAS < 25 mm; aprepitant 61%, control 56%).

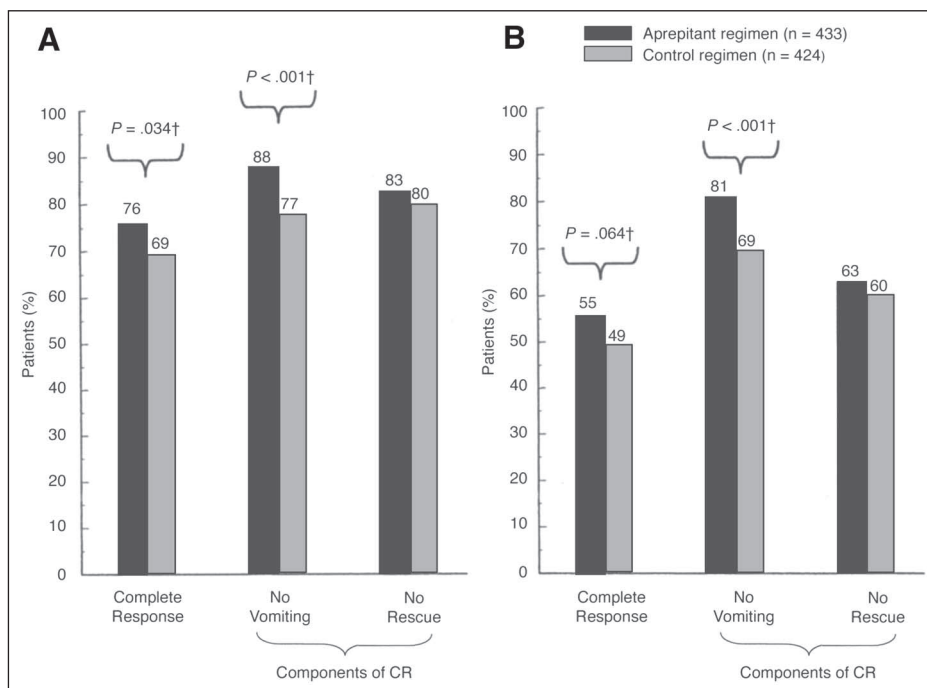
**Tolerability**

The DSMB met several times throughout the course of the study to review summaries of the safety data; no issues

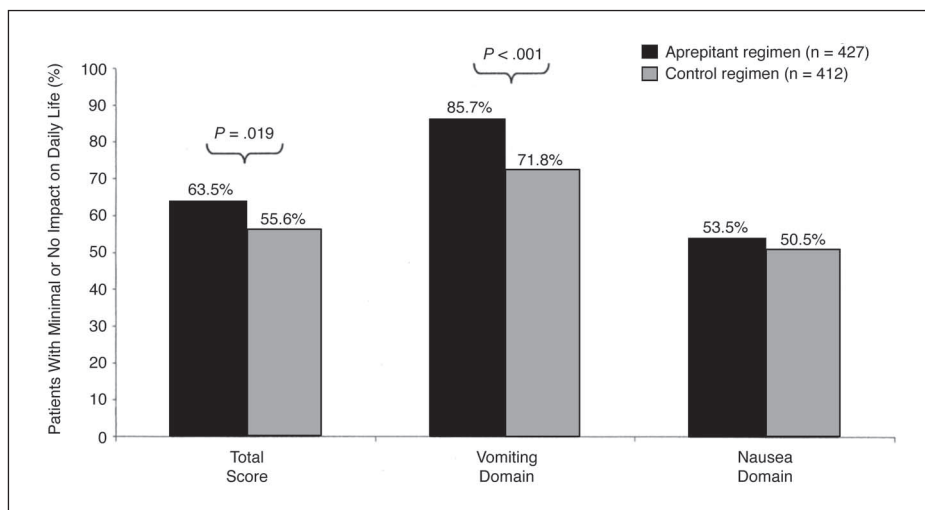
were detected. The percentage of patients with clinical AEs or laboratory abnormalities during the study is listed in Table 3. The only appreciable difference in tolerability was a slightly higher rate of constipation in the control group (18.0% v 12.3%) and slightly more dyspepsia in the aprepitant group (8.4% v 4.9%). The incidence of investigator-reported febrile neutropenia was identical for both treatments (2.1%).

**DISCUSSION**

This large clinical trial in women with breast cancer addressed the potential utility of an NK<sub>1</sub>-receptor antagonist as a component of a regimen with a corticosteroid and a 5-HT<sub>3</sub>-receptor antagonist for the prevention of CINV induced by cyclophosphamide-based chemotherapy. As seen in previous trials with cisplatin-based HEC,<sup>12-14,20</sup> addition of aprepitant to an antiemetic regimen containing a 5-HT<sub>3</sub>-receptor antagonist, ondansetron, and a corticosteroid, dexamethasone, was superior to ondansetron and dexamethasone alone in the proportion of patients achieving a complete response overall after one cycle of MEC. This study is notable for MEC antiemetic studies in terms of the homogeneity of the patient population and also the uniformity of the emetogenic stimulus provided. Although the chemotherapy regimen that patients received in this study is defined as moderately emetogenic, the relatively low complete response rate of 42% in the control group clearly underscores the need for improved therapy in this patient



**Fig 3.** Graph showing percentage of patients with complete response (CR; no vomiting and no use of rescue therapy) from 0-24 hours (acute) and 24-120 hours (delayed) after initiation of the first cycle of chemotherapy. (†) *P* values are for between-group differences (for summary purposes only). Black bars = aprepitant; gray bars = control.



**Fig 4.** Bar graph showing percentage of patients with an average score of  $> 6$  on a 7-point scale on the Functional Living Index-Emesis questionnaire, signifying minimal or no impact of emesis on daily living, for total score overall and vomiting and nausea domains. Black bars = aprepitant; gray bars = control.

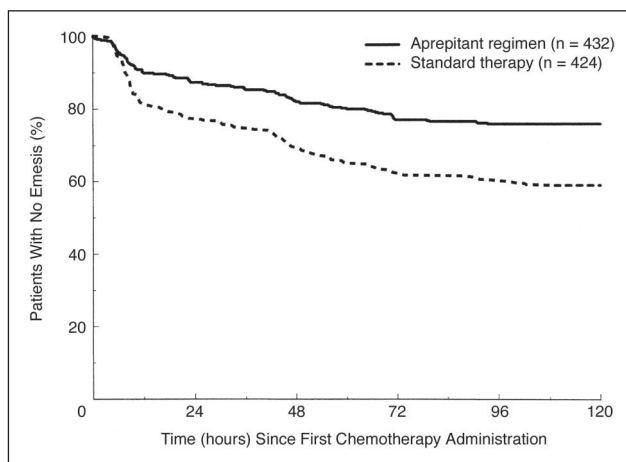
population. The choice of comparator regimen, ondansetron bid and dexamethasone on day 1 followed by ondansetron bid on days 2 and 3, was much more rigorous than the regimens in recently published MEC antiemetic studies<sup>21,22</sup> in which the control arm treatment regimen consisted of only a single dose of a 5-HT<sub>3</sub>-receptor antagonist; hence, this study is particularly relevant to clinical practice.

Aprepitant clearly provided significant benefit (eight percentage points during 120 hours;  $P < .015$ ) throughout the acute and delayed phases. That the response was not as pronounced as that seen with the addition of aprepitant in patients receiving cisplatin-based chemotherapy is probably a consequence of the potency of the emetogenic stimulus of the combination of cyclophosphamide and an anthracycline in women, who are known to be more susceptible to CINV. It is also worth noting that the control therapy group was administered a 5-HT<sub>3</sub>-receptor antago-

nist beyond day 1, whereas the experimental aprepitant group did not, and there is evidence that administering 5-HT<sub>3</sub>-receptor antagonists beyond 24 hours can enhance the control of delayed-phase symptoms associated with MEC.<sup>8,23</sup>

The aprepitant effect was more pronounced early ( $\approx 6$  hours) in the acute phase in this study, whereas the aprepitant effect was more notable later ( $\approx 18$  hours) in the cisplatin HEC studies.<sup>12-14,20</sup> This may be a consequence of the mechanism of CINV caused by the chemotherapy used in the present study, or of the patient population (almost exclusively women). Importantly, though, the benefit is clearly present throughout the acute and delayed phases thereafter. The precise transition between the acute and delayed phases at 24 hours is arbitrary, however, and has no clearly proven scientific basis; it is also of questionable clinical relevance.<sup>24</sup>

In the present study, the most pronounced effect of aprepitant was seen in the prevention of vomiting, with an absolute difference of 17% between the aprepitant regimen and the control group. Patients frequently cite vomiting as a major concern of chemotherapy treatment, and hence, the aprepitant benefit has important clinical significance. There



**Fig 5.** Time to first emesis. Kaplan-Meier curves for time-to-first emesis from start of chemotherapy administration overall (0 to 120 hours) for cycle 1. Solid line = aprepitant regimen; dashed line = control regimen.

**Table 3.** Overall Summary of Clinical AEs and Neutrophil Counts

AE	% of Patients	
	Aprepitant Regimen (n = 438)	Control Regimen (n = 428)
Drug-related*	21.5	19.6
Serious	3.4	4.2
Discontinuations due to AE	1.6	1.2
Febrile neutropenia	2.1	2.1

Abbreviation: AE, adverse events.

\*Those considered by the investigator to be possibly, probably, or definitely related to study drug.



was no significant effect of aprepitant on nausea, though it is important to note again that the control group received active therapy with ondansetron for all 3 days, whereas the aprepitant group received ondansetron only on day 1. The more pronounced effect of aprepitant and 5-HT<sub>3</sub>-receptor antagonists on the prevention of vomiting compared with nausea implies that serotonin and substance P may play a relatively more important role in the pathogenesis of vomiting than of nausea, and that other neurotransmitters may also be involved in the pathogenesis of these symptoms, especially nausea.

As seen in previous studies, the aprepitant regimen was well tolerated. Earlier studies assessing aprepitant use for HEC<sup>13,14</sup> showed a trend toward more fatigue with the aprepitant regimen than with the control regimen; this was not seen in the present MEC study. The only notable differences between the treatment groups were a greater incidence of constipation from the control regimen, a predictable consequence of multiple-day 5-HT<sub>3</sub>-receptor antagonist therapy, and more dyspepsia from the aprepitant regimen. There was no evidence of any AEs caused by potential interactions of aprepitant with chemotherapy agents used in the current study; however, caution is advised when administering aprepitant to patients treated with chemotherapy metabolized via CYP3A4.

In conclusion, the addition of aprepitant to an antiemetic regimen of ondansetron and dexamethasone resulted in significantly better prevention of CINV than ondansetron and dexamethasone alone in patients receiving moderately emetogenic chemotherapy. These and previous similar results for cisplatin-based highly emetogenic chemotherapy demonstrate the utility of aprepitant as a component of a regimen for the prevention of CINV across a range of emetogenic chemotherapies. The data provide a foundation for refinement of the aprepitant regimen, potentially by increasing the duration of administration of the concomitant 5-HT<sub>3</sub>-receptor antagonist and/or the corticosteroid to further improve the prevention of CINV associated with MEC. Additional clinical trials are warranted.

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### Appendix

Participating investigators of the Aprepitant MEC Study Group were: Anita Aggarwal, Francis P. Arena, Roy Beveridge, Ruemu Birhiray, Albert Brady, Elmer Brestan, Goran Broketa, Patrick Byrne, Elber Camacho, Robert Carroll, Javier Cassinello Espinosa, Veena Charu, Sant Chawla, Naveed

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