

Addition of the Neurokinin 1 Receptor Antagonist Aprepitant to Standard Antiemetic Therapy Improves Control of Chemotherapy-Induced Nausea and Vomiting

Results from a Randomized, Double-Blind, Placebo-Controlled Trial in Latin America

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 054 Study Group

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Supported by Merck Research Laboratories.

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Received January 6, 2003; revision received February 26, 2003; accepted March 2, 2003.

BACKGROUND. Aprepitant is a novel neurokinin 1 (NK₁) antagonist that has been shown to improve control of chemotherapy-induced nausea and vomiting (CINV) when added to a standard antiemetic regimen of a 5-hydroxytryptamine-3 antagonist plus a corticosteroid. The authors sought to evaluate further the efficacy and tolerability of aprepitant plus standard therapy in a large clinical trial.

METHODS. This was a multicenter, randomized, double-blind, placebo-controlled, parallel-groups, Phase III study. Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy were randomized to receive 1 of 2 treatment regimens; the standard therapy group received intravenous ondansetron 32 mg and oral dexamethasone 20 mg on Day 1, and oral dexamethasone 8 mg twice daily on Days 2–4. The aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg on Day 1; oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on Days 2–3; and oral dexamethasone 8 mg on Day 4. Patients recorded episodes of emesis, use of rescue therapy, and severity of nausea in a diary. A modified intent-to-treat approach was used to analyze the efficacy data. The primary endpoint was complete response (no emesis and no rescue therapy) during the 5-day period post-cisplatin. Treatment comparisons were made using logistic regression models, and reported adverse events and physical and laboratory assessments were used to assess tolerability.

RESULTS. A total of 523 patients were evaluated for efficacy, and 568 patients were evaluated for safety. During the 5 days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group (163 of 260 patients) versus 43.3% in the standard therapy group (114 of 263 patients; $P < 0.001$). For Day 1, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group ($P < 0.001$); for Days 2–5, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group ($P < 0.001$). The overall incidence of adverse events was similar between the 2 treatment groups (72.8% in the aprepitant group [206 of 283 patients] and 72.6% in the standard therapy group [207 of 285 patients]) as were rates of serious adverse events, discontinuations due to adverse events, and deaths.

CONCLUSIONS. In patients with cancer who are receiving high-dose cisplatin-based chemotherapy, therapy consisting of aprepitant (125 mg on Day 1 and 80 mg on Days 2–3) plus a standard regimen of ondansetron and dexamethasone provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated. *Cancer* 2003;97:3090–8.

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DOI 10.1002/cncr.11433

KEYWORDS: aprepitant, neurokinin 1 antagonist, antiemetic, substance P, clinical trial.

Cancer patients, nurses, and physicians have noted that nausea and vomiting are among the most feared and distressing side effects of chemotherapy.¹⁻³ Currently, the most effective antiemetic regimen for the prevention of these symptoms consists of a 5-hydroxytryptamine-3 (5-HT₃) antagonist (administered prior to chemotherapy only) and a corticosteroid (administered prior to chemotherapy and continued for a total of 4–5 days). Continued administration of a 5-HT₃ antagonist for several days after chemotherapy also has been recommended by consensus treatment guidelines published by the Multinational Association of Supportive Care in Cancer and the American Society of Clinical Oncology, although the benefits of this strategy have not been demonstrated clearly in patients receiving highly emetogenic chemotherapy.⁴⁻⁸

Even with the appropriate use of currently available antiemetic therapy, however, 50% of patients who receive highly emetogenic chemotherapy such as cisplatin still suffer from chemotherapy-induced nausea and vomiting (CINV): approximately 25% of patients experience CINV in the first 24 hours after infusion of chemotherapy (known as the *acute phase of CINV*), and up to 50% of patients suffer from CINV after the first 24 hours postchemotherapy (referred to as the *delayed phase of CINV*).^{1,4,5,9} Thus, there clearly is a need for improvement in protection against CINV, particularly during the delayed phase.

Aprepitant (EMEND®; Merck, Whitehouse Station, NJ) is a potent and selective oral nonpeptide antagonist of the neurokinin-1 (NK₁) receptor, which is known to play a role in CINV.¹⁰ In early clinical trials, aprepitant given in combination with a 5-HT₃ antagonist and dexamethasone enhanced protection against acute emesis and strikingly improved protection against delayed emesis. The combination provided sustained protection over multiple cycles of chemotherapy and was generally well tolerated.¹¹⁻¹⁸ The present study, which was conducted in Latin America, describes results from 1 of 2 Phase III trials that were designed to demonstrate conclusively the efficacy and tolerability of the aprepitant regimen in a large population of patients with cancer. The other study, the results of which will be the subject of a separate publication, was conducted in North America, Europe, Australia, Taiwan, and South Africa.

MATERIALS AND METHODS

Design

This multicenter, randomized, double-blind, parallel-group, placebo-controlled trial was conducted at 18 centers in a total of 8 Latin American countries (Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Peru, and Venezuela). All patients provided written

informed consent to participate in the study, which was approved by the ethical review board of each participating site.

Patients

Cisplatin-naïve patients over 18 years of age who had histologically confirmed solid tumors, a Karnofsky score ≥ 60 , and who were scheduled to receive a chemotherapy regimen that included cisplatin ≥ 70 mg/m² were eligible to participate. Female patients of childbearing potential were required to have a negative β -human chorionic gonadotropin test result. The primary exclusion criteria included the following: abnormal laboratory values (including white blood count $< 3000/\text{mm}^3$ and absolute neutrophil count $< 1500/\text{mm}^3$, platelet count $< 100,000/\text{mm}^3$, aspartate aminotransferase $> 2.5 \times$ the upper limit of normal, alanine aminotransferase $> 2.5 \times$ the upper limit of normal, bilirubin $> 1.5 \times$ the upper limit of normal, or creatinine $> 1.5 \times$ the upper limit of normal); active infection or uncontrolled disease that, in the opinion of the investigator, excluded the patient for safety reasons; a planned regimen of multiple-day, cisplatin-based chemotherapy in a single cycle; radiation therapy to the abdomen or pelvis within 1 week prior to Day 1 of the study or between Day 1 and Day 6; or moderately or highly emetogenic chemotherapy on the 6 days prior to and/or after the day of cisplatin infusion. Additional chemotherapeutic agents of high emetogenicity (Hesketh level ≥ 3) were permitted only on Day 1, and additional antiemetics were prohibited within 2 days prior to Day 1 or between Day 1 and Day 6 of the study, unless such medications were given as rescue therapy for established nausea or vomiting.

Procedures

A computer-generated randomization schedule was used to assign eligible patients to 1 of 2 treatment groups, which were stratified by gender and use of concomitant emetogenic chemotherapy categorized by the Hesketh classification.¹⁹ The standard therapy regimen consisted of intravenous ondansetron 32 mg and oral dexamethasone 20 mg on Day 1, followed by oral dexamethasone 8 mg twice daily on Days 2–4. The aprepitant regimen consisted of oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on Day 1; oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on Days 2 and 3; and oral dexamethasone 8 mg on Day 4. The dosing regimen was modified from that used in earlier clinical studies, in which patients typically received aprepitant on Days 1–5. Because earlier studies suggested that dosing beyond Day 3 may not be necessary, aprepitant was given for 3 days rather than 5 days

in the present study, using doses previously determined to be the most appropriate.²⁰ In addition, a pharmacokinetic study in healthy subjects found that aprepitant increased dexamethasone levels by approximately 2-fold.²¹ Because differential exposure to dexamethasone theoretically may confound the interpretation of the efficacy and safety profile of aprepitant, the dexamethasone dose was reduced by 50% in the aprepitant group in the current study, so that dexamethasone plasma exposure would be generally similar in both treatment groups.

One hour prior to cisplatin, patients received either aprepitant or placebo. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone. One exception to this regimen was that patients receiving docetaxel or paclitaxel in addition to cisplatin were given dexamethasone at a dose of 20 mg at 12 hours, and again at 6 hours, prior to infusion of paclitaxel or docetaxel, but did not receive dexamethasone 30 minutes prior to cisplatin. Cisplatin was then infused over a period of ≤ 3 hours, with the beginning of infusion designated as T_{zero} (hours).

Assessments

During Days 1–5, patients used a diary to report the date and time of episodes of emesis (expulsion of stomach contents through the mouth) or retching (a nonproductive attempt to vomit), with distinct episodes defined as those separated by at least 1 minute. The use of rescue therapy (i.e., any medication taken to treat established nausea or vomiting) also was recorded. Patients rated nausea daily with a 100-mm horizontal visual analogue scale (VAS). Patients also completed a Functional Living Index-Emesis (FLIE) questionnaire on Day 6, which captured information about the effect of CINV on patients' daily lives.^{22,23} On Days 2–6, study site personnel made daily telephone contact with patients to confirm that they were taking study medications appropriately and were maintaining accurate records. Tolerability was assessed by physical examinations including vital signs, weight, laboratory tests, and electrocardiograms. Patients returned to the clinic between Day 6 and Day 8 and again between Day 19 and Day 29. Completion of the study was defined as completion of the visit between Day 19 and Day 29, and cessation of the study at any other time was considered a discontinuation. Patients had the option of enrolling in a multiple cycles extension of the study for up to 5 additional cycles of chemotherapy. Findings from this extension will be the subject of a separate publication.

Statistical Analysis

All patients who received cisplatin, took study drug, and had at least one posttreatment assessment during Cycle 1 were included in the modified intent-to-treat approach used to analyze the data. The proportion of patients who achieved a complete response (defined as no emetic episodes and no use of rescue therapy) in the overall study period (Days 1–5) was the primary endpoint of the efficacy analysis. The following other endpoints were also analyzed: 1) no emesis, 2) no use of rescue therapy, 3) complete protection (no emesis, no rescue therapy, and no significant nausea [VAS score < 25 mm]), 4) total control (no emesis, no rescue therapy, and no nausea [VAS score < 5 mm]), 5) the impact of CINV on daily life (as measured by a FLIE total score > 108)²³, 6) no significant nausea (VAS score < 25 mm), and 7) no nausea (VAS score < 5 mm).

The response criteria outlined above were applied to the acute phase (Day 1), the delayed phase (Days 2–5), and the overall study period (Days 1–5), except for the no nausea and no significant nausea endpoints, for which an acute-phase analysis was not planned. The impact of CINV on daily life was assessed only for the overall 5-day study period. For treatment comparisons, logistic regression models were used that included terms for treatment, gender, use of concomitant chemotherapy (Hesketh level ≥ 3), and that used a two-sided significance level of 5%. Treatment-by-factor interactions were assessed at the 10% significance level with logistic models and, if appropriate, with the Gail and Simon test at the 5% significance level to assess whether any interactions were qualitative.

A 15-percentage-point difference was anticipated between the treatment groups for the primary endpoint of complete response in the overall phase. The study had 90% power to detect this difference based on a 2-sided test at a significance level $\alpha = 0.05$, with a sample size of 470 evaluable patients.

Tolerability assessments were performed using tabulations of adverse events and protocol specified laboratory parameters, and included all patients who received cisplatin and at least 1 dose of study medication. The Fisher exact test was used to make between-treatment comparisons for the proportions of patients with the following: 1) any adverse events, 2) drug-related adverse events (i.e., determined by the investigator to be possibly, probably, or definitely related to study drug), 3) serious adverse events (according to a standard regulatory definition), and 4) discontinuation of treatment due to an adverse event.

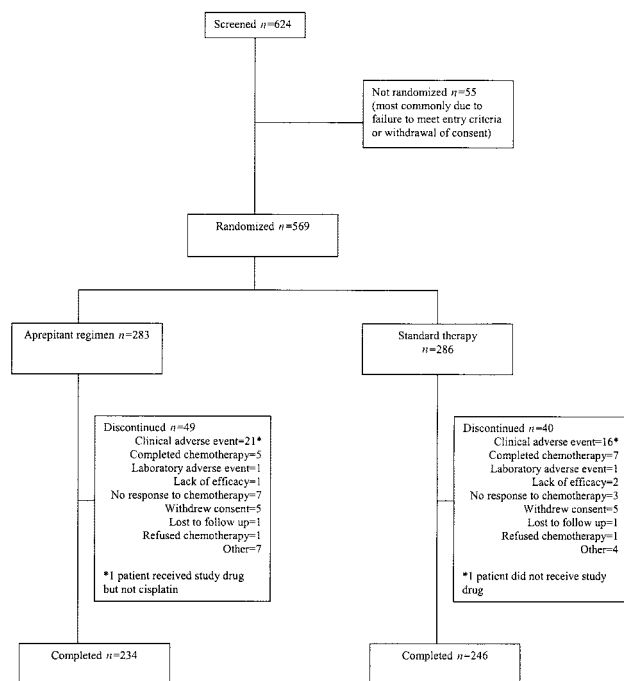


FIGURE 1. Study flow chart.

Because increases in febrile neutropenia and infection-related adverse events associated with aprepitant were noted in a previous trial and were hypothesized to be due to increases in dexamethasone in patients taking aprepitant,²⁰ specific treatment comparisons were made with respect to these types of adverse events. In addition, due to the known moderate inhibitory effect of aprepitant on the CYP3A4 enzyme,²⁴ serious adverse events also were tabulated according to the concomitant use of CYP3A4-metabolized chemotherapeutic agents.

RESULTS

Patients

Of the 624 patients screened, 569 patients were randomized (Fig. 1). Of these, 2 patients were excluded from the safety and efficacy analyses because they did not receive both cisplatin and at least 1 dose of study drug. Also excluded from the efficacy analyses were 2 patients who failed to provide efficacy data and 40 patients from 1 site whose efficacy data were considered unreliable after an audit; these patients were included in the safety assessments. Reasons for discontinuation were similar between the treatment groups (Fig. 1).

Table 1 shows that patient baseline characteristics, including known risk factors for CINV (female gender, history of alcohol use, motion sickness, or prior CINV), were similar between the treatment

groups, although a slightly greater incidence of a history of morning sickness was noted in the aprepitant group, and a slightly greater incidence of a history of chemotherapy was observed in the standard therapy group. Primary diagnoses were generally similar between groups, although there was a slightly greater incidence of malignancies of the eyes, ears, nose, and throat in the aprepitant group (11% vs. 6%) and a greater incidence of urogenital cancer in the standard therapy group (42% vs. 35%). The most common primary diagnoses were respiratory tract and urogenital system cancer (Table 1).

Efficacy

For the primary endpoint of complete response (no emesis and no use of rescue therapy), the aprepitant regimen was statistically superior to standard therapy in the overall study period (62.7% vs. 43.3% in the overall phase, a 19 percentage-point difference; $P < 0.001$), as well as in separate analyses of the acute phase (82.8% vs. 68.4%; $P < 0.001$), and particularly in the delayed phase (67.7% vs. 46.8%; $P < 0.001$) (Fig. 2). Interactions between treatment and gender and between treatment and concomitant chemotherapy were not significant ($P > 0.10$), indicating that in the analyses, response rates could be combined across these prespecified stratification factors.

Table 2 shows results for other endpoints. The percentage of patients in the aprepitant group who had no emesis was significantly greater compared with the standard therapy group for all three phases of the study. In addition, a significantly greater percentage of patients in the aprepitant group experienced no nausea (VAS score < 5 mm) in the delayed phase (52.7% vs. 39.9% with standard therapy) and in the overall 5-day study period (48.8% vs. 38.8% with standard therapy; $P < 0.05$ for both comparisons). The aprepitant group also had a greater percentage of patients with complete protection (no emesis, no rescue, and no significant nausea [VAS < 25 mm]) in the acute phase (80.0% vs. 64.6% with standard therapy), the delayed phase (60.9% vs. 44.1%), and the overall 5-day study period (55.6% vs. 40.7%; $P < 0.01$ for all 3 comparisons). Results were similar for other endpoints; in the majority of comparisons, the aprepitant regimen was statistically superior to standard therapy (Table 2).

Kaplan–Meier curves of time to first emesis showed that in the overall study period, patients who received the aprepitant regimen fared significantly better than patients who received only standard therapy ($P < 0.001$; log-rank test) (Fig. 3). The treatment groups began to differ noticeably about 16 hours post-cisplatin administration, after which fewer patients

TABLE 1
Patient Baseline Characteristics by Treatment Group

Characteristic	Aprepitant regimen (n = 283 patients)	Standard therapy (n = 286 patients)
Female (%)	48	49
Age (yrs)		
Mean \pm SD	54 \pm 13	53 \pm 14
Range	18–82	18–81
Race (%)		
Black	5	6
White	31	28
Other	64	66
Use of concurrent emetogenic chemotherapy (% of patients) ^a	17	17
Cisplatin dose (mg/m ²)		
\geq 70–100 (% of patients)	82	82
Mean dose	81	81
Alcoholic drinks/week (% of patients)		
0	84	87
1–10	14	12
>10	2	1
History (% of patients)		
Morning sickness	10	7
Motion sickness	4	4
Chemotherapy	7	10
CINV	5	6
Primary cancer diagnosis (% of patients)		
Respiratory	37	36
Urogenital	35	42
Eyes/ears/nose/throat	11	6
Other	17	16

SD: standard deviation; CINV: chemotherapy-induced nausea and vomiting.

^a Hesketh level \geq 3.

had emesis in the aprepitant group compared with the standard therapy group.

The FLIE questionnaire showed that significantly more patients in the aprepitant group (74.7%) reported minimal or no impact of CINV on daily life, compared with patients on standard therapy (63.5%).

To evaluate the relationship between acute emesis and delayed emesis, patients were categorized according to whether or not they had acute emesis, and the resulting 2 categories of patients were then compared in terms of their delayed responses. Regardless of which treatment they received, patients who were emesis-free in the acute phase were more likely to remain emesis-free in the delayed phase, compared with patients who had acute emesis. Within each category of acute response, the two treatment groups were then compared. In the subset of patients who had no emesis in the acute phase, the percentage of patients who were also emesis-free in the delayed phase was greater in the aprepitant group (79.3%) compared with the standard therapy group (64.6%). In the subset of patients who had acute emesis, the percentage of patients who were emesis-free in the de-

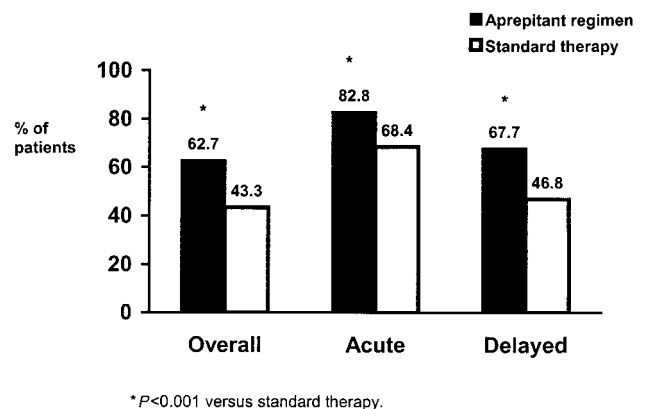


FIGURE 2. Illustration of the percentages of patients in each treatment group who achieved a complete response (no emesis and no rescue therapy) during the overall study period (Days 1–5), during the acute phase (Day 1), and during the delayed phase (Days 2–5). For the aprepitant regimen, there were 261 patients in the acute phase and 260 patients in the delayed and overall phases; for the standard therapy regimen, there were 263 patients.

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

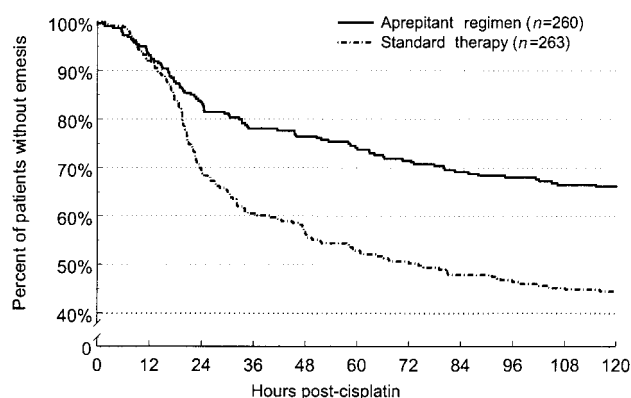
Treatment group	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
	Aprepitant regimen (n = 260 patients) ^a	Standard therapy (n = 263 patients) ^a	Aprepitant regimen (n = 261 patients) ^a	Standard therapy (n = 263 patients) ^a	Aprepitant regimen (n = 260 patients) ^a	Standard therapy (n = 263 patients) ^a
No emesis	66 ^b	44	84 ^b	69	72 ^b	48
No rescue	82 ^b	73	96 ^b	90	83 ^c	74
Complete protection	56 ^b	41	80 ^b	65	61 ^b	44
Total control	44 ^b	32	64	57	50 ^b	34
No nausea	49 ^c	39	n/p	n/p	53 ^b	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.

^a Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.

^b $P < 0.01$ compared with standard therapy.

^c $P < 0.05$ compared with standard therapy.

**FIGURE 3.** Percent of patients without emesis.

layed phase was also greater in the aprepitant group (32.6%) compared with the standard therapy group (12.2%).

Tolerability

Tolerability analyses included all patients who received cisplatin and at least 1 dose of study drug. Table 3 shows a summary of adverse events that were reported up to 14 days after treatment. The overall incidences of clinical adverse events, drug-related clinical adverse events, serious clinical adverse events, laboratory adverse events, drug-related laboratory adverse events, and discontinuations due to clinical adverse events were similar between the treatment groups (Table 3). Of the 24 deaths that occurred, 13 deaths (4.6%) occurred in the aprepitant group, and 11 deaths (3.9%) occurred in the standard therapy group, with adverse events involving the respiratory system cited most commonly as the cause of death (6 patients in the aprepitant group and 5 patients in the standard

therapy group). None of the events that resulted in death was considered drug-related by the investigator. Serious adverse events occurred in 11.0% of patients in the aprepitant group and in 9.8% of patients in the standard therapy group. Of these, only three adverse events were considered by the investigator as possibly, probably, or definitely related to study drug (1 event of worsening diabetes mellitus and 1 event of hyperglycemia in the standard therapy group; 1 event of disorientation in the aprepitant group). It is noteworthy that the patient in the aprepitant group had been treated with furosemide for 6 days prior to the onset of the disorientation, and laboratory tests on Day 6 revealed hypokalemia and elevated blood urea nitrogen, suggesting that the patient may have been dehydrated. The most commonly reported serious clinical adverse events in the aprepitant group and the standard therapy group, respectively, included neutropenia (1.8% vs. 2.1%), dehydration (1.8% vs. 0.7%), septic shock (1.1% vs. 0.7%), dyspnea (1.1% vs. 0.7%), and respiratory insufficiency (1.8% vs. 0.4%).

Eighty-three patients on the aprepitant regimen and 71 patients on standard therapy experienced laboratory adverse events. No serious laboratory adverse events or deaths related to laboratory adverse events were reported. In addition, 1 patient in each treatment group discontinued therapy due to laboratory adverse events; however, those events were neither serious nor drug-related. Although no formal statistical comparisons were made with regard to patterns of National Cancer Institute (NCI) toxicity Grade 3 or Grade 4 changes in laboratory values, inspection of the data indicated that decreases in hematologic laboratory values (anemia, leukopenia, neutropenia, and thrombocytopenia) measured at posttreatment visits were similar between treatment groups. One patient in the

TABLE 3
Summary of Adverse Events

Percent of patients	Aprepitant regimen (n = 282 patients) ^a	Standard therapy (n = 285 patients) ^a
With 1 or more clinical adverse events	72.7	72.6
With drug-related clinical adverse events ^b	19.5	14.4
With serious clinical adverse events	11.0	9.8
Discontinued due to a clinical adverse event	7.1	5.3
With 1 or more laboratory adverse events	29.6	25.2
With drug-related laboratory adverse events	5.7	3.9
With most common clinical adverse events ^c		
Anorexia	15.2	14.0
Asthenia/fatigue	18.4	14.0
Constipation	12.4	12.3
Diarrhea	12.1	10.5
Headache	9.9	11.6
Nausea	14.5	14.4
Vomiting	8.9	12.6

^a For laboratory data, n = 280 patients in the aprepitant group, and n = 282 patients in the standard therapy group.

^b Adverse events that were considered by the investigator to be possibly, probably, or definitely related to study drug.

^c Greater than or equal to 10% in at least one treatment group. There were no statistically significant ($P > 0.1$) risk differences between treatments for groupings of adverse events. Statistical testing was not performed for individual common adverse events. Nausea and vomiting were considered adverse events if they occurred after Day 5 of the study, or at any time if they were determined by the investigator to be serious or drug-related or if they resulted in discontinuation.

aprepitant group and no patients in the standard therapy group had NCI toxicity Grade 3 or Grade 4 elevations in serum creatinine levels, and the patterns of NCI toxicity Grade 3 or Grade 4 elevations in liver function tests (alanine aminotransferase or aspartate aminotransferase) were also similar across treatment groups (1 patient in the aprepitant group; 4 patients in the standard therapy group).

The investigators reported that 3 patients (0.5%) had febrile neutropenia (1 patient [0.4%] on the aprepitant regimen and 2 patients [0.7%] on standard therapy). A between-treatment comparison for serious adverse events related to infection (including pneumonia and sepsis) also showed no significant difference ($P = 0.323$). A total of 328 patients (164 patients in the aprepitant group and 164 patients in the standard therapy group) received CYP3A4-metabolized chemotherapy agents, including etoposide, vinca alkaloids, and taxanes. The incidence of serious clinical adverse events in this subpopulation of 328 patients was greater in the aprepitant group (26 of 164 patients) compared with the standard therapy group (14 of 164 patients). The corresponding incidence of serious adverse events among the 240 patients who did not receive CYP3A4-metabolized chemotherapy was

greater in the standard therapy group (11.6% vs. 4.2% in the aprepitant group).

DISCUSSION

Although 5-HT₃ antagonists have been particularly effective for the control of symptoms that occur in the acute phase (especially up to approximately 16 hours postcisplatin), they have not been as effective against symptoms that occur in the delayed phase (> 24 hours) in patients taking highly emetogenic chemotherapy.²⁵ In the present study, the aprepitant regimen protected approximately two-thirds of patients from emesis after they received highly emetogenic chemotherapy and enabled them to avoid the use of rescue therapy during the 5 days after cisplatin, whereas treatment of the control group with the best currently available standard therapy protected less than half of patients. The difference of 19 percentage points is substantially greater than the 10 percentage-point difference generally considered to be clinically relevant,²⁶ representing a clearly meaningful benefit. In the assessments of complete response over specific periods after cisplatin, the aprepitant regimen provided a substantial improvement of 14 percentage points over standard therapy in the prevention of acute symptoms, and a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV.

Because patients were considered treatment failures if they either vomited or took rescue medication to alleviate nausea, the complete response endpoint not only reflects control of emesis but also indirectly reflects control of nausea. For the overall phase as well as for the acute and delayed phases, the use of rescue medication for the relief of established vomiting or nausea was statistically significantly greater in the standard therapy group compared with the aprepitant group. Furthermore, the rates of no significant nausea and no nausea were consistently greater with the aprepitant regimen. Moreover, for the more stringent endpoint of complete protection, which incorporated assessments for no emesis, no use of rescue, and no significant nausea (VAS score < 25 mm), the percentages of patients who achieved this endpoint were significantly greater in the aprepitant group for all 3 time periods evaluated. The aprepitant group also achieved significantly greater success for the most stringent endpoint of total control, which incorporated a very rigorous nausea assessment (no nausea; VAS score < 5 mm), for the entire 5-day period after chemotherapy and especially for the delayed phase.

The improved prevention of delayed CINV with aprepitant is especially noteworthy in light of the limited efficacy of currently available therapy after Day 1

postcisplatin.^{5,9,27} In time-dependent assessments of percentages of patients without emesis, the benefit of aprepitant was first distinguishable from about 16 hours postcisplatin. The frequency of delayed emesis, as expected, was lower in patients who had no emesis in the acute phase, irrespective of treatment group. However, patients who were emesis-free in the acute phase were much more likely to remain emesis-free in the delayed phase if they received the aprepitant regimen. Similarly, among patients who had acute emesis, those on the aprepitant regimen were much more likely than those on standard therapy to be emesis-free in the delayed phase. Hence, the superiority of the aprepitant regimen in preventing delayed emesis cannot be described solely as a carry-over effect from the acute period, because its superior delayed efficacy was demonstrated consistently, regardless of efficacy in the acute phase.

The incidences and profiles of clinical and laboratory adverse events were comparable between the treatment groups and were consistent with a population of patients with cancer who were receiving high-dose cisplatin-based chemotherapy. The incidence of deaths was similar between groups, and there were no deaths that the investigators considered related to study drug. The incidences and types of serious adverse events also were similar between treatment groups, with a small number considered drug-related (1 patient in the aprepitant group; 2 patients in the standard therapy group). Adverse events that were more frequent in the aprepitant group included asthenia/fatigue, diarrhea, dizziness, and hiccups. The percentage of patients who discontinued the study due to a clinical adverse event was greater in the aprepitant group, although the overall number of discontinuations was low (7.1% in the aprepitant group; 5.3% in the standard therapy group), and only 1 discontinuation was considered drug-related. Moreover, no statistically significant between-treatment risk difference was noted for discontinuations due to adverse events.

No notable trends were observed in the protocol specified laboratory data analyses; and, although slightly more serious adverse events of hematologic toxicity were associated with the aprepitant group, categorization for protocol specified laboratory safety tests using the NCI common toxicity criteria did not reveal any differences between the treatment groups for hematologic parameters. Prespecified analyses for serious adverse events of infection and for febrile neutropenia revealed no statistically significant between-treatment differences. Among the 58% of patients in the study who received concomitant treatment with CYP3A4 metabolism-dependent chemotherapeutic agents such as etoposide, vinorelbine, paclitaxel, and

docetaxel the incidence of serous adverse events was greater in the aprepitant group compared with the standard therapy group. By contrast, among patients who did not receive such concomitant treatments, the incidence of serious adverse events was lower with the aprepitant regimen. Similar comparisons performed in another Phase III trial with the same design showed that the incidence of serious adverse events in aprepitant-treated patients was similar regardless of concomitant treatment with CYP3A4 metabolism-dependent chemotherapy; these findings will be the subject of a separate publication.

The addition of aprepitant to a standard therapy regimen consisting of a 5-HT₃ antagonist plus dexamethasone improved the control of CINV associated with highly emetogenic cisplatin-based chemotherapy in the overall study period, in the acute phase, and particularly in the delayed phase. The aprepitant regimen was generally well tolerated, with incidences and overall patterns of clinical and laboratory adverse events similar to those associated with standard therapy. The time course and magnitude of improved control of emesis achieved with aprepitant support the hypothesis that superior control of CINV involves the blockade of substance P-mediated nausea and vomiting. Aprepitant represents an important medical advance that can substantially enhance the supportive care of patients with cancer who receive highly emetogenic chemotherapy.

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