

The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin—The Aprepitant Protocol 052 Study Group

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Purpose: In early clinical trials with patients receiving highly emetogenic chemotherapy, the neurokinin antagonist aprepitant significantly enhanced the efficacy of a standard antiemetic regimen consisting of a type-three 5-hydroxytryptamine antagonist and a corticosteroid. This multicenter, randomized, double-blind, placebo-controlled phase III study was performed to establish definitively the superiority of the aprepitant regimen versus standard therapy in the prevention of chemotherapy-induced nausea and vomiting (CINV).

Patients and Methods: Patients receiving cisplatin ≥ 70 mg/m² for the first time were given either standard therapy (ondansetron and dexamethasone on day 1; dexamethasone on days 2 to 4) or an aprepitant regimen (aprepitant plus ondansetron and dexamethasone on day 1; aprepitant and dexamethasone on days 2 to 3; dexamethasone on day 4). Patients recorded nausea and vomiting episodes in a diary. The primary end point was complete response (no

emesis and no rescue therapy) on days 1 to 5 postcisplatin, analyzed by a modified intent-to-treat approach. Treatment comparisons were made using logistic regression models. Tolerability was assessed by reported adverse events and physical and laboratory assessments.

Results: The percentage of patients with complete response on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), as were the percentages on day 1, and especially on days 2 to 5 ($P < .001$ for all three comparisons).

Conclusion: Compared with standard dual therapy, addition of aprepitant was generally well tolerated and provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy.

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NAUSEA AND vomiting are among the most feared and distressing adverse effects of chemotherapy from a patient's standpoint.¹⁻³ Substantial progress has been made in improving the control of chemotherapy-induced nausea and vomiting (CINV) due in large part to the introduction of selective type-three 5-hydroxytryptamine (5-HT₃) receptor antagonists (RAs) approximately 10 years ago.⁴ Nevertheless, CINV remains suboptimally controlled for a significant number of cancer patients

receiving chemotherapy. Remaining challenges include symptoms occurring more than 24 hours after chemotherapy (delayed CINV), symptoms during repeat cycles of chemotherapy, and symptoms associated with very high-dose chemotherapy.⁵⁻¹¹ Significant progress in preventing CINV is likely to depend on the introduction of new and effective antiemetic agents.

Substance P is a regulatory peptide found in areas of the CNS (including the nucleus tractus solitarius and area postrema) and the gastrointestinal tract (vagal afferents) believed to be essential components of the emetic reflex.¹²⁻¹⁴ The actions of substance P are mediated through the neurokinin-1 (NK₁) receptor, a G-protein receptor coupled to the inositol phosphate signal transduction pathway. In animal models, selective nonpeptide antagonists of the NK₁ receptor have demonstrated antiemetic activity against central, peripheral, and combined emetic stimuli. Penetration of these agents into the CNS seems to be essential to their antiemetic action.¹⁵

Aprepitant (EMEND®; Merck and Co Inc, Whitehouse Station, NJ) represents a new class of antiemetic. It is a potent, selective, CNS-penetrant, oral nonpeptide antagonist of the NK₁ receptor. In the same preclinical models used to predict the clinical utility of the 5-HT₃ RAs, selective NK₁ RAs have also demonstrated potent ability to inhibit emesis induced by chemotherapy. Unlike the 5-HT₃ RAs, NK₁ RAs have demonstrated efficacy against both early (acute) and later (delayed) emesis,

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and have been effective against a much broader spectrum of emetic stimuli.^{16,17} Cisplatin is considered to be the single most emetogenic chemotherapeutic agent, and in the absence of preventive antiemetic therapy, it induces emesis in nearly all patients.^{8,12,18} In the assessment of preventive antiemetic therapy, cisplatin is considered a useful benchmark, both because of its emetogenicity and because the efficacy of antiemetic agents against cisplatin-induced vomiting has reliably predicted antiemetic efficacy against less emetogenic chemotherapy.⁴ In early-phase clinical studies that included more than 1,200 cancer patients receiving their first cisplatin-based chemotherapy, aprepitant demonstrated enhanced protection against acute emesis (occurring in the first 24 hours after chemotherapy) when combined with dual therapy consisting of a 5-HT₃ RA and dexamethasone.^{19,20} In addition, aprepitant significantly improved the prevention of delayed emesis when compared as a single-agent with placebo, or when combined with dexamethasone, compared with dexamethasone alone.^{21,22} This study was conducted to confirm these findings in a large phase III study, as well as to refine the dose regimen and to examine further the tolerability profile of aprepitant.

The study design was modified from that used in earlier (phase II) studies, in which aprepitant was given either on day 1 only or from days 1 to 5. In these studies, although continued dosing with aprepitant beyond day 1 was advantageous, dosing beyond day 3 did not seem to confer additional benefit. In the present study, aprepitant was therefore given for 3 days rather than 5 days, using doses previously determined to be the most appropriate.²³ In addition, a pharmacokinetic study in healthy subjects found that aprepitant increased dexamethasone levels approximately two-fold.²⁴ Because differential exposure to dexamethasone could theoretically confound the interpretation of the efficacy and safety profile of aprepitant, a 50% reduction of the dexamethasone dose was made in the aprepitant group in the current study so that dexamethasone plasma exposure would be similar in both study groups.

PATIENTS AND METHODS

Design

All patients gave written informed consent to participate in this randomized, double-blind, parallel-group, placebo-controlled trial conducted in accordance with applicable ethical requirements and conducted at a total of 56 centers (15 in the United States and 41 in 14 other countries).

Patients

Cisplatin-naïve patients older than 18 years with a Karnofsky score \geq 60 who were scheduled to receive their first cycle of chemotherapy including cisplatin \geq 70 mg/m² were enrolled. All patients had histologically confirmed solid tumors. Female patients of childbearing potential were required to have a negative beta human chorionic gonadotropin test result. The primary exclusion criteria included the following: the patient was a current user of illicit drugs or had signs of current alcohol abuse; abnormal laboratory values (including WBC $<$ 3,000/mm³ and absolute neutrophil count $<$ 1,500/mm³, platelet count $<$ 100,000/mm³, AST $>$ 2.5 \times upper limit of normal [ULN], ALT $>$ 2.5 \times ULN, bilirubin $>$ 1.5 \times ULN, or creatinine $>$ 1.5 \times ULN); uncontrolled disease for which, in the opinion of the investigator, the patient should be excluded for safety reasons; multiple-day

cisplatin-based chemotherapy in a single cycle; or radiation therapy to the abdomen or pelvis within 1 week before study day 1 or between days 1 to 6.

Procedures

Patients who met entry criteria were assigned to one of two treatment groups according to a computer-generated random assignment schedule created by an assistant statistician otherwise uninvolved with the study. Randomization was stratified by sex and use of concomitant emetogenic chemotherapy as categorized by the Hesketh classification.¹⁸ Patients in the standard therapy group received intravenous ondansetron 32 mg and oral dexamethasone 20 mg on day 1, followed by oral dexamethasone 8 mg twice daily on days 2 to 4. Patients in the aprepitant group received 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. Placebo capsules matching aprepitant, and placebo tablets matching dexamethasone were used to maintain blinding, and drug disclosure information was provided in separate sealed envelopes identified by allocation number.

One hour before cisplatin, patients received either aprepitant or placebo. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone. Cisplatin was then infused during a period of \leq 3 hours, with the start of infusion designated as T₀ (hours). Patients receiving docetaxel or paclitaxel in addition to cisplatin were premedicated with two doses of dexamethasone 20 mg before paclitaxel or docetaxel infusion. Additional chemotherapeutic agents of high emetogenicity (Hesketh level \geq 3) were permitted only on day 1; patients could not have received such agents within 6 days before day 1 or within 6 days following day 1. Patients could not receive additional antiemetics within 2 days before day 1 or between days 1 and 6 of the study, unless such medications were given as rescue therapy for established nausea or vomiting.

Assessments

On day 1 and throughout the study, patients recorded their response to treatment in a diary, including the date and time of emetic episodes, with distinct episodes defined as those separated by at least 1 minute. The use of rescue therapy, defined as any medication taken to treat established nausea or emesis, was also recorded. Patients rated nausea daily using a 100-mm horizontal visual analog scale (VAS). On day 6, patients also completed a Functional Living Index-Emesis (FLIE) questionnaire to assess the effect of nausea and emesis on quality of life during the 5-day study period.^{25,26} On days 2 to 6, daily telephone contact was made by study site personnel to confirm that patients were taking study medications appropriately and maintaining accurate records. Tolerability was monitored by physical examinations, including vital signs and weight measurement, laboratory studies, and ECGs. Patients returned to the clinic between days 6 and 8, and again between days 19 and 29. Completion of the study was defined as completion of the visit between days 19 and 29; cessation of the study at any other time was considered a discontinuation.

Statistical Analysis

The sponsor managed the data and performed the analyses for this study. The primary end point for the efficacy analysis was the proportion of patients with complete response, defined as no emetic episodes and no rescue therapy (ie, medication taken for established nausea or vomiting) overall (days 1 to 5). Other end points included no emesis, no use of rescue therapy, complete protection (no emesis, no rescue therapy, and no significant nausea [VAS score, $<$ 25 mm]), total control (no emesis, no rescue therapy, and no nausea [VAS score, $<$ 5 mm]), the impact of CINV on daily life (as measured by a FLIE total score $>$ 108),²⁶ no nausea (VAS score, $<$ 5 mm); and no significant nausea (VAS score, $<$ 25 mm).

A modified intent-to-treat approach, which included all patients who received cisplatin, took study drug, and had at least one posttreatment assessment, was used to analyze the data. The response criteria outlined earlier were applied to the overall 5-day study period and also to the acute and delayed phase components, although analysis was not planned for acute

phase nausea. Treatment comparisons were made using logistic regression models that included terms for treatment, sex, use of concomitant chemotherapy (Hesketh level ≥ 3), and region (United States *v* other countries). Sex and use of concomitant chemotherapy were prespecified baseline stratification factors, whereas region was prespecified as a factor of interest. All comparisons used a two-sided significance level of 5%. Tests of significance were based on the logistic regression model, and nominal *P* values were reported. For the same factors, treatment-by-factor interactions were assessed at the 10% significance level with logistic models, and if an interaction was present, Gail and Simon's test at the 5% significance level was used to evaluate whether any interactions were qualitative.

Regarding the primary end point of complete response, a 15-percentage point difference was anticipated between the treatment groups for the overall 5-day study period. Based on a sample size of 470 patients, the study had 90% power to detect this difference based on a two-sided test with a significance level of $\alpha = .05$.

For tolerability, between-treatment comparisons were made using Fisher's exact test for the percentages of patients with the following: any adverse events, any drug-related adverse events (ie, those considered by the investigator to be possibly, probably, or definitely related to study drug), any

serious adverse events (according to a standard regulatory definition), and discontinuation of treatment due to an adverse event. Because of the known moderate inhibitory effect of aprepitant on the CYP3A4 enzyme, serious adverse events were also tabulated according to the concomitant use of CYP3A4-metabolized chemotherapeutic agents.

RESULTS

Patients

Of the 562 patients screened, 530 were randomized, and 521 (260 patients in the aprepitant group and 261 patients in the standard therapy group) were included in the efficacy analyses (Fig 1). Five patients were excluded from both the efficacy and the safety analyses because they did not receive cisplatin and at least one dose of study drug. An additional four patients who did not provide any efficacy assessments, despite having received cisplatin and study drug, were also excluded from the efficacy analyses. Reasons for discontinuation were similar between the treatment groups (Fig 1).

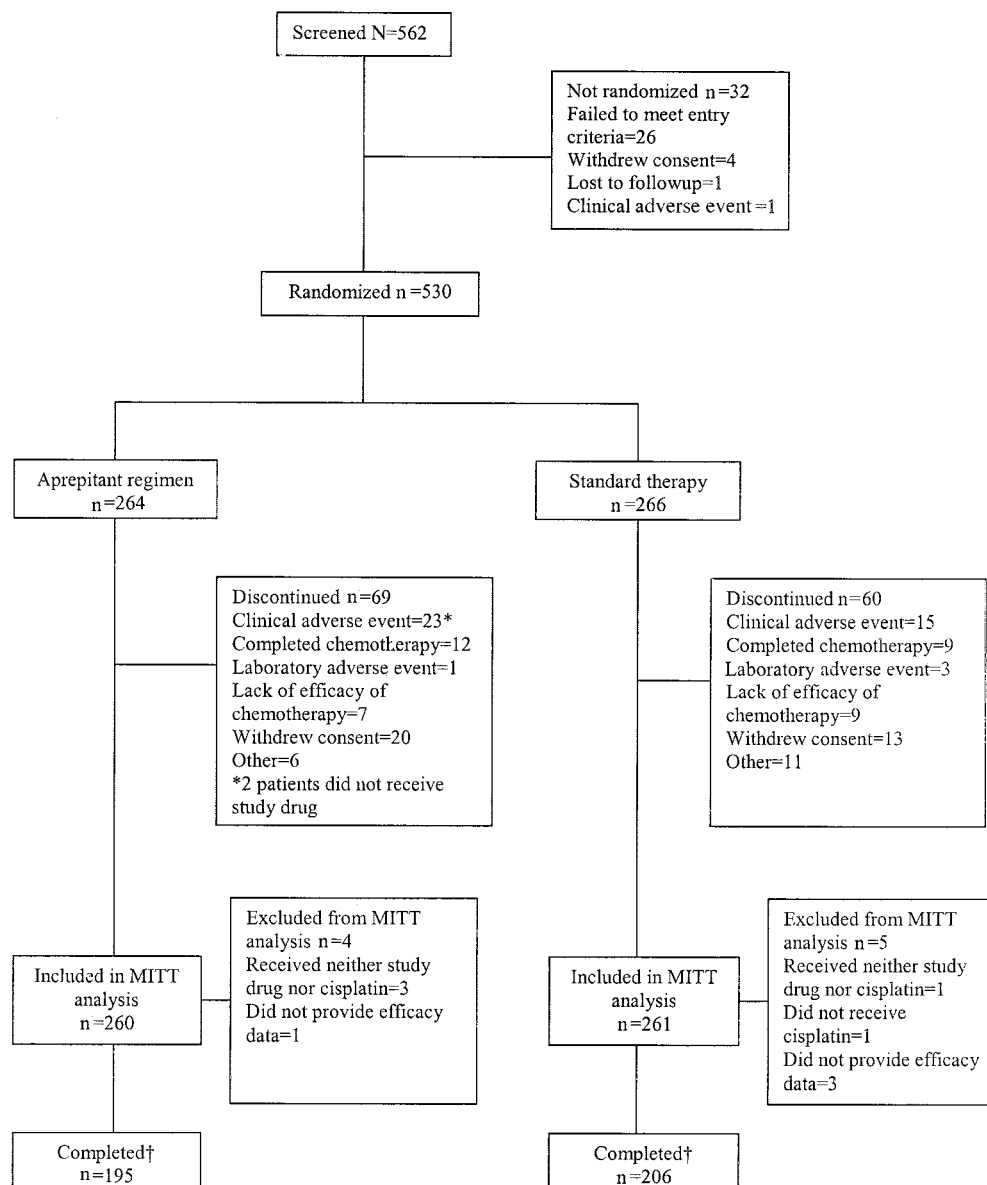


Fig 1. Study flow chart. † Patient completed the day 19 to 29 visit; MITT, modified intent-to-treat.

Patient baseline characteristics, including known risk factors for CINV (being female, history of alcohol use, morning sickness, motion sickness, or prior CINV), were similar between the treatment groups (Table 1). Likewise, the cisplatin doses and primary cancer diagnoses were similar, with respiratory-system cancer the most common (Table 1).

Efficacy

For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had complete response overall and in the acute and delayed phases. The aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; $P < .001$), as well as in separate analyses of both the acute phase (89.2% v 78.1%; $P < .001$), and even more notably, the delayed phase (75.4% v 55.8%; $P < .001$). Interactions between treatment and region, or treatment and concomitant chemotherapy, were not significant ($P > .10$), though a significant treatment-by-sex interaction was noted ($P < .001$). Within the aprepitant group, the percentages of females (77.6%) and males (69.8%) with complete response overall were similar, whereas in the standard therapy group overall, the

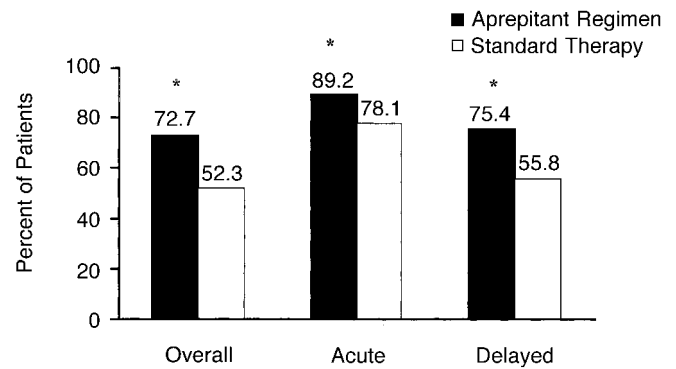


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: $n = 259$ in the acute phase, and $n = 260$ overall and in the delayed phase. For standard therapy, $n = 260$. * $P < .001$ versus standard therapy.

percentage of females who had complete response (38.8%) was less than that of males with complete response (60.5%). This interaction was not found to be significantly qualitative ($P > .5$, by Gail and Simon's test), indicating that the two treatment groups could be combined across sexes for the statistical analyses.

The aprepitant regimen was also statistically superior in all comparisons for the secondary and exploratory end points of no emesis, no rescue therapy, and complete protection (Table 2). In comparisons for total control, no nausea, and no significant nausea, results for the aprepitant regimen were consistently numerically higher, though the differences did not reach statistical significance (Table 2). For the end point of complete protection, which accounts for both emesis and nausea, the aprepitant regimen was significantly better than standard therapy in all three study periods.

Figure 3 shows Kaplan-Meier curves depicting percentages of patients without emesis in each treatment group overall. Significantly more time elapsed until the first emetic episode in patients on the aprepitant regimen, compared with those on standard therapy ($P < .001$, based on the log-rank test). The treatment groups did not differ discernibly for the first 12-16 hours, but thereafter, fewer patients had emesis in the aprepitant group than in the standard therapy group.

Logistic regression analysis of the results of the FLIE questionnaire showed that significantly more patients in the aprepitant group (74.0%) reported minimal or no impact of CINV on daily life as compared with those on standard therapy (64.3%) and as measured by the total score (analysis not adjusted for multiplicity).

To investigate the influence of response to acute emesis on delayed emesis, patients were categorized according to their emetic response in the acute phase (those with acute emesis and those without), and their delayed responses were then compared. Regardless of the treatment 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 did have acute emesis. Within each category of acute response, a comparison was then made between the two treatment groups. In the subset

Table 1. Patient Baseline Characteristics by Treatment Group

	Aprepitant Regimen (n = 264)	Standard Therapy (n = 266)
Sex, female	37	38
Age, years		
Mean	59	58
SD	12	12
Range	18-84	19-83
Race		
Black	4	2
White	89	92
Other	7	6
Use of concurrent emetogenic chemotherapy*	15	16
Region (United States)	22	22
Cisplatin dose		
≥ 70 -100 mg/m ² †	70	70
Mean dose, mg/m ²	81	80
Alcoholic drinks/week		
0	58	58
1-10	24	23
> 10	17	15
History of morning sickness	7	5
History of motion sickness	7	4
History of chemotherapy	15	14
History of CINV	7	5
Primary cancer diagnosis		
Respiratory	44	40
Urogenital	21	25
Other	35	35

NOTE. All data are given as percent of patients, unless otherwise noted.

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

*Hesketh level ≥ 3 .

†Some patients received cisplatin at doses less than 70 mg/m². The slight variability in dose occurred due to use of different formulas at different sites for the calculation of body-surface area, and due to fluctuation in body weight for individual patients between enrollment and administration of chemotherapy. All patients received cisplatin ≥ 50 mg/m².

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

Treatment Group	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
	Aprepitant Regimen (n = 260)†	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)†	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)†	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

**P* < .05 versus standard therapy (significance based on logistic regression model).

†*P* < .01 versus standard therapy (significance based on logistic regression model).

‡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 end points.

§Analysis not planned.

of patients who were emesis-free in the acute phase, the percentage of patients who were also emesis-free in the delayed phase was higher in the aprepitant group (86.3%) compared with the standard therapy group (69.4%). In the subset of patients who had acute emesis, the percentage of patients who were emesis-free in the delayed phase was also higher in the aprepitant group (30.8%) versus the standard therapy group (18.5%).

Tolerability

All patients who received cisplatin and at least one dose of study drug were included in the statistical analyses for safety. Table 3 summarizes adverse events 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 adverse events, were similar between the treatment groups (Table 3). Of the 16 deaths that occurred, seven (2.7%) were in the aprepitant group, and nine (3.4%) were in the standard therapy group. None of the adverse events resulting in death were considered drug-related

by the investigator. Cardiac arrest was the most commonly reported adverse event resulting in death (two patients in the aprepitant group, and one patient in the standard therapy group). Three serious adverse events were considered possibly, probably, or definitely drug-related by the investigator: one event in the aprepitant group (perforating duodenal ulcer considered by the investigator to be related to dexamethasone) and two events in the standard therapy group (chills and leg pain in one patient, and hyponatremia in another). The most commonly reported serious adverse events in the aprepitant and standard therapy groups, respectively, included dehydration (1.9% v 1.1%), febrile neutropenia (2.3% v 1.9%), neutropenia (2.7% v 0%), and thrombocytopenia (1.5% v 0%). The most common adverse events that seemed to show an increase following the aprepitant regimen versus standard therapy were asthenia or fatigue,

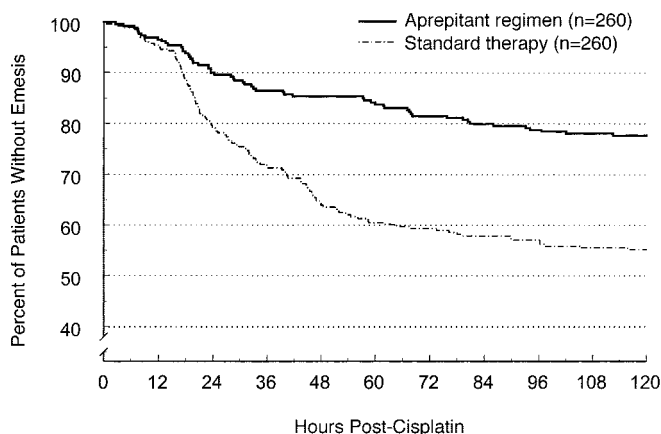
Table 3. Summary of Adverse Events

	Aprepitant Regimen (n = 261)	Standard Therapy (n = 264)
% of patients		
With ≥ 1 clinical adverse event	65.1	61.4
With drug-related* clinical adverse events	14.6	11.0
With serious clinical adverse events	16.1	17.0
Discontinued due to a clinical adverse event	8.0	5.3
With ≥ 1 laboratory adverse event	14.0	13.5
With drug-related laboratory adverse events	2.3	1.2
With most common clinical adverse events†		
Asthenia/fatigue	17.2	9.5
Constipation	8.0	12.1
Hiccups	13.8	6.8
Nausea‡	10.7	8.7

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

†≥ 10% in at least one treatment group. There were no statistically significant (*P* > .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 determined by the investigator to be serious, be drug-related, or result in discontinuation.

**Fig 3. Kaplan-Meier curves demonstrating percentages of patients without emesis during the 120-hour study period.**

hiccups, and nausea occurring after day 5 (or serious/drug-related/causing discontinuation; Table 3).

The percentages of patients with laboratory adverse events were similar in the two groups (Table 3). Serious laboratory adverse events were reported for two patients (hypokalemia and hyponatremia in one patient in the aprepitant group, and decreased hemoglobin in one patient in the standard therapy group), but none of these was fatal or considered drug-related. In addition, four patients (one on the aprepitant regimen, and three on standard therapy) discontinued treatment due to laboratory adverse events, but these events were neither serious nor drug-related. Although no formal statistical comparisons were made with regard to patterns of National Cancer Institute (NCI) common toxicity criteria 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 across treatment groups. Five patients in the aprepitant group and one patient in the standard therapy group had an NCI toxicity grade 3 or grade 4 elevation in liver function tests (ALT or AST), and the pattern of NCI toxicity grade 3 or grade 4 elevations in serum creatinine was also similar across treatment groups (zero patients in the aprepitant group, and three patients in the standard therapy group).

The three most common CYP3A4-metabolized chemotherapeutic agents given in this study were etoposide, vinorelbine, and paclitaxel. A total of 185 patients received such agents (100 in the aprepitant group, and 85 in the standard therapy group). The incidence of serious clinical adverse events in this population was low and generally comparable between treatment groups, as was the corresponding incidence among patients who did not receive CYP3A4-metabolized chemotherapy. A similar assessment was made for laboratory adverse events, which found that among patients who had received such concomitant chemotherapy, none had a serious laboratory adverse event. Thirteen patients (2.5%) were reported by investigators to have had febrile neutropenia (8 patients [3.1%] on the aprepitant regimen, and 5 patients [1.9%] on standard therapy), and a comparison of patients who had serious adverse events related to infection (including pneumonia, cystitis, and sepsis) showed no significant between-treatment difference.

DISCUSSION

Despite substantial recent progress, at least 50% of patients experience CINV following an initial cycle of cisplatin-based chemotherapy, and substantially more have CINV during repeat cycles of chemotherapy. In early clinical trials of aprepitant or its intravenously administered prodrug L-758,298, the NK₁ RA aprepitant consistently demonstrated efficacy in preventing cisplatin-induced delayed emesis, and when combined with the current antiemetic standard of a 5-HT₃ RA and dexamethasone, aprepitant improved antiemetic outcomes as compared with standard therapy.¹⁹⁻²² In the present study, which was the first phase III study of a selective NK₁ RA for the prevention of CINV in cancer patients, the addition of a 3-day regimen of aprepitant significantly improved complete response as com-

pared with standard therapy throughout the acute and delayed phases. The magnitude of the benefit associated with the aprepitant regimen (greater than the minimum difference of 10 percentage points, generally considered to be clinically relevant²⁷) was clearly both statistically significant and clinically meaningful, and was particularly marked during the delayed phase. Moreover, this benefit was observed even in the context of good results achieved in the control group, which were similar to the high response rates seen in other trials of standard therapy.²⁸⁻³⁰ Because patients were considered treatment failures if they had any emesis or took rescue medication to alleviate nausea, the primary complete response end point not only reflected control of emesis, but also functioned as a surrogate index of nausea control. It is important to note that the dexamethasone regimen was adjusted between the treatment groups in this study so that the plasma exposure to dexamethasone would be comparable between groups, thereby eliminating a potentially confounding effect of differential dexamethasone exposure on efficacy or tolerability findings.

Regardless of the specific end point, response rates overall and in the acute and delayed phases were consistently greater for the aprepitant group than for standard therapy. In particular, for the end points of no emesis, complete response, and complete protection (which incorporates both emesis and nausea assessment), the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV. Although the groups did not differ statistically for total control, no nausea, and no significant nausea, rates for these end points were consistently numerically higher in the aprepitant group. The higher response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, indicate that aprepitant provided some benefit against nausea as well as emesis.

The effectiveness of aprepitant in improving the control of delayed emesis is particularly noteworthy given the modest efficacy of current treatment approaches.^{4,8,11} Several trials have assessed the effect of adding a 5HT₃ antagonist to a corticosteroid for management of delayed CINV, but these studies have failed to demonstrate a definitive benefit of this practice.^{5-7,31,32} These equivocal findings emphasize the importance of the especially robust efficacy aprepitant provides in the delayed phase. In an assessment of the time to first emetic event, the benefit of aprepitant became apparent approximately 12 to 16 hours after the initiation of cisplatin. Thus, the therapeutic effect of aprepitant is evident during the later portion of the acute phase and the delayed phase, the period during which acute failures associated with standard therapy typically occur.³³ The time course of the antiemetic effect of aprepitant is particularly opportune, in that patients are protected at a time when they are especially vulnerable to failure on standard antiemetic therapy.

Regardless of treatment group, the frequency of delayed emesis was lower in patients who had been emesis-free in the acute phase. However, these 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 was not a carryover effect from the acute period because superior delayed efficacy was consistently demonstrable irrespective of efficacy in the acute phase.

The superiority of aprepitant was also evident irrespective of sex. It should be noted that although the superiority of the aprepitant regimen was observed in this study to be of greater magnitude in female patients, results of a second study of identical design did not produce a similar magnitude of difference relative to sex³⁴; the finding in this study is therefore of limited inferential value. A more detailed discussion of the effect of the aprepitant regimen on risk factors for CINV will be the subject of a separate publication.

The incidence and profile of adverse events were consistent with a population of patients with cancer receiving highly emetogenic cisplatin-based chemotherapy, and were comparable between the treatment groups. A low overall incidence of deaths was observed, with slightly fewer deaths in the aprepitant group, and none of the deaths was considered drug-related. The incidence and types of serious adverse events were also similar in both treatment groups, and the number of discontinuations was low with only a small number due to drug-related adverse events. Adverse events that were more frequent in the aprepitant group included asthenia or fatigue, hiccups, and nausea occurring after day 5 or with certain characteristics as determined by the investigator. No noteworthy trends were observed in the protocol-specified laboratory data analyses, and categorization of protocol-specified laboratory safety tests using the NCI common toxicity criteria did not reveal any differences between the treatment groups for hematologic parameters.

The safety profile did not suggest that the aprepitant regimen enhanced the toxicity of chemotherapy or increased the susceptibility to infection. In another phase III trial identical to the present study, the incidence of serious adverse events was higher in the aprepitant group for patients receiving concomitant

CYP3A4 metabolized chemotherapy.³⁴ In contrast, in the current study, the incidence of adverse events was similar irrespective of concomitant treatment with chemotherapeutic agents that are dependent on CYP3A4 metabolism, such as docetaxel, paclitaxel, and etoposide, among others. Prespecified analyses for serious adverse events of infection and febrile neutropenia revealed no significant between-treatment differences.

In summary, the addition of aprepitant to a regimen of ondansetron and dexamethasone improved the control of CINV associated with highly emetogenic cisplatin-based chemotherapy throughout the acute and delayed phases. The aprepitant regimen was generally well tolerated, with incidences and overall patterns of clinical and laboratory adverse experiences similar to those associated with standard therapy. The superior control of CINV achieved with aprepitant combined with a 5HT₃ RA and a corticosteroid represents an important medical advance that can substantially enhance the supportive care of cancer patients, and further limit the impact of CINV on daily life.

APPENDIX

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following authors or their immediate family members have indicated a financial interest as follows. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock: Alexandra D. Carides, Merck; Scott Reines, Merck; Judith K. Evans, Merck; Klaus Beck, Merck; Kevin J. Horgan, Merck. Acted as a consultant within the last 2 years: Paul J. Hesketh, Merck; Steven M. Grunberg, Merck; Ronald de Wit, Merck; Richard J. Gralla, Merck; Fausto Roila, Merck; David G. Warr, Merck; Sant P. Chawla, Merck. Performed contract work within the last 2 years: Paul J. Hesketh, Merck; Steven M. Grunberg, Merck; Ronald de Wit, Merck; Richard J. Gralla, Merck; Fausto Roila, Merck; David G. Warr, Merck; Sant P. Chawla, Merck. Received more than \$2,000 a year from a company for either of the last 2 years: Paul J. Hesketh, Merck; Steven M. Grunberg, Merck; Ronald de Wit, Merck; Richard J. Gralla, Merck; Fausto Roila, Merck; Scott Reines, Merck; Mary E. Elmer, Merck; Judith K. Evans, Merck; Alexandra D. Carides, Merck; Juliana Ianus, Merck; Kevin J. Horgan, Merck.

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