Establishing the Dose of the Oral NK_1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting

Sant P. Chawla, M.D.[1]
Steven M. Grunberg, M.D.[2]
Richard J. Gralla, M.D.[3]
Paul J. Hesketh, M.D.[4]
Cindy Rittenberg, R.N., M.N., A.O.C.N.[5]
Mary E. Elmer, M.S.N., C.R.N.P.[6]
Carrie Schmidt, B.S.[6]
Arlene Taylor, M.S.[6]
Alexandra D. Carides, Ph.D.[6]
Judith K. Evans, M.D.[6]
Kevin J. Horgan, M.D.[6]

[1] Century City Hospital, Los Angeles, California.

[2] University of Vermont, Burlington, Vermont.

[3] New York Lung Cancer Alliance, New York, New York.

[4] St. Elizabeth's Medical Center, Brighton, Massachusetts.

[5] Rittenberg Oncology Consulting, Metairie, Louisiana.

[6] Merck Research Laboratories, West Point, Pennsylvania.

Presented as an abstract in preliminary form at the 37th annual meeting of the American Society of Clinical Oncologists, San Francisco, California, May 12–15, 2001.

This study was funded by Merck Research Laboratories, manufacturers of aprepitant.

Dr. Chawla, Dr. Grunberg, Dr. Gralla, and Dr. Hesketh are consultants for Merck and Company, Inc.; Ms. Elmer, Ms. Schmidt, Ms. Taylor, Dr. Carides, Dr. Evans, and Dr. Horgan are employees of and potentially hold stock in Merck and Company, Inc.

Address for reprints: Sant P. Chawla, M.D., Century City Hospital, 2080 Century Park East, Suite 1511, Los Angeles, CA 90067; Fax: (310) 201-6685; E-mail: santchawla@aol.com.

Received October 7, 2002; revision received December 10, 2002; accepted December 17, 2002.

BACKGROUND. The neurokinin-1 antagonist aprepitant (EMEND™; Merck Research Laboratories, West Point, PA) has been shown to reduce chemotherapy-induced nausea and vomiting when it is given with a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone. The current study sought to define the most appropriate dose regimen of oral aprepitant.

METHODS. This multicenter, randomized, double-blind, placebo-controlled study was conducted in patients with cancer who were receiving initial cisplatin ($\geq$ 70mg/m^2) and standard antiemetic therapy (intravenous ondansetron plus oral dexamethasone). Patients were randomized to receive standard therapy plus either aprepitant 375 mg on Day 1 and 250 mg on Days 2–5, aprepitant 125 mg on Day 1 and 80 mg on Days 2–5, or placebo. Due to an apparent interaction with dexamethasone suggested by pharmacokinetic data obtained while the study was ongoing, the aprepitant 375/250 mg dose was discontinued and replaced with aprepitant 40 mg on Day 1 and 25 mg on Days 2–5, and a new randomization schedule was generated. Patients recorded nausea and emesis in a diary. The primary endpoint was complete response (no emesis and no rescue therapy), which was analyzed using an intent-to-treat approach with data obtained after the dose adjustment. Treatment comparisons were made using logistic regression models. Tolerability was assessed by reported adverse events and physical and laboratory assessments, and included all available data.

RESULTS. The percentages of patients who achieved a complete response in the overall study period were 71.0% for the aprepitant 125/80-mg group (n = 131 patients), 58.8% for the aprepitant 40/25-mg group (n = 119 patients), and 43.7% for the standard therapy group (n = 126 patients; $P < 0.05$ for either aprepitant regimen vs. standard therapy). Rates for Day 1 were 83.2% for the aprepitant 125/80-mg group, 75.6% for aprepitant 40/25-mg group, and 71.4% for the standard therapy group ($P < 0.05$ for aprepitant 125/80 mg vs. standard therapy), and rates on Days 2–5 were 72.7% for the aprepitant 125/80-mg group, 63.9% for the aprepitant 40/25-mg group, and 45.2% for the standard therapy group ($P < 0.01$ for either aprepitant group vs. standard therapy). The efficacy of the aprepitant 375/250-mg regimen was similar to that of the aprepitant 125/80-mg regimen. The overall incidence of adverse events was generally similar across treatment groups: 85% in the aprepitant 375/250-mg group (n = 34 patients), 76% in the aprepitant 125/80-mg group (n = 214 patients), 71% in the aprepitant 40/25-mg group (n = 120 patients), and 72% in the standard therapy group (n = 212 patients), with the exception of a higher incidence of infection in the aprepitant 125/80-mg group (13%) compared with the standard therapy group (4%).

CONCLUSIONS. When it was added to a standard regimen of intravenous ondansetron and oral dexamethasone in the current study, aprepitant reduced chemotherapy-induced nausea and vomiting and was generally well tolerated, although increases in infection were noted that were assumed to be due to elevated dexamethasone levels as a result of the pharmacokinetic interaction. The aprepitant 125/80-mg regimen had the most favorable benefit:risk profile. ***Cancer* 2003;97:2290–300.**

DOI 10.1002/cncr.11320

KEYWORDS: antiemetic, substance P, neurokinin, clinical trial.

Despite recent therapeutic advances in the prevention of chemotherapy-induced nausea and vomiting (CINV), these symptoms are still regarded by patients with malignant disease as among the most important complications of chemotherapy.[1–3] Traditionally, the efficacy of antiemetic therapies has been evaluated in patients receiving cisplatin, which is considered the single most emetogenic chemotherapeutic agent.[4] In the absence of preventive antiemetic therapy, higher doses of cisplatin (> 50 mg/m^2) evoke acute vomiting (within 24 hours of administration) in virtually 100% of patients and delayed vomiting (2–7 days postadministration) in approximately 70–90% of patients.[5,6] In the assessment of the efficacy of antiemetic agents, cisplatin is a useful benchmark not only because of its predictable emetogenicity but also because it has been possible to translate reliably the antiemetic effects of agents on cisplatin-induced nausea and vomiting to the nausea and vomiting caused by other chemotherapy regimens.[7]

A number of treatments are available for patients with CINV. Single-agent therapy with a 5-hydroxytryptamine-3 receptor antagonist ($5HT_3$ RA) has been shown to prevent acute vomiting in 40–60% of patients receiving higher doses of cisplatin (> 50 mg/m^2); and when dexamethasone is coadministered, the proportion of patients without acute vomiting has been observed to improve to 60–90%.[7] The various 5-HT_3 RAs are essentially equivalent in terms of both their efficacy and their side-effect profiles, irrespective of the route of administration.[7] However, in contrast to the efficacy demonstrated in the treatment of patients with acute cisplatin-based CINV, it has been shown that 5-HT_3 RAs are less clearly effective in the delayed phase ($>$ 24–120 hours after cisplatin).[6,7]

The relatively poor efficacy of existing treatments for the prevention of delayed CINV has prompted the development of therapies with a different mechanism of action, such as neurokinin-1 (NK_1) receptor antagonists (NK_1 RAs). The NK_1 receptor is the preferential site of action of the neuropeptide substance P. The identification of both NK_1 receptors and substance P in regions of the brainstem that are believed to mediate the emesis reflex raised the possibility that substance P, acting via NK_1 receptors, is involved in the pathogenesis of emesis.[8–10] This concept was supported by the finding that NK_1 RAs such as aprepitant (EMEND™; Merck Research Laboratories, West Point, PA) prevented emesis induced by chemotherapy in standard preclinical models.[11–13]

Aprepitant, a potent and selective, nonpeptide, brain-penetrant NK_1 RA with a long duration of action, has been shown to reduce emesis in patients receiving chemotherapy regimens based on high-dose cisplatin.[10] Dosing with aprepitant (also known as L-754,030 or MK-0869), either as monotherapy or in combination with corticosteroids prior to the initiation of cisplatin-based chemotherapy, reduced acute emesis, although 5-HT_3 RAs appeared to be at least as effective, if not more so, than aprepitant alone in the acute phase.[14–16] However, Navari et al. reported that coadministration of aprepitant and dexamethasone plus a 5-HT_3 RA on the day of chemotherapy provided superior control even compared with the control achieved with the currently recommended dual-therapy regimen of a 5-HT_3 antagonist plus dexamethasone; subsequent findings by Campos et al. confirmed those results.[15,17] Furthermore, dosing with aprepitant prior to initiation of cisplatin-based chemotherapy provided particularly good control of delayed vomiting, and continued dosing with aprepitant on subsequent days improved control of both vomiting and nausea.[15,17]

Thus, early clinical data suggest that the NK_1 RA aprepitant represents a new class of antiemetic therapy with a distinctive efficacy profile: it has been shown that aprepitant enhances the prevention of both acute CINV and delayed CINV, with particular efficacy in the delayed phase. The objective of the current study was to identify an appropriate dosing regimen of aprepitant, when given in conjunction with a 5-HT_3 antagonist and dexamethasone, in patients receiving high-dose cisplatin-based chemotherapy. The study also further assessed the efficacy and tolerability profiles of aprepitant.

MATERIALS AND METHODS

Design

This multicenter, randomized, double-blind, parallel-group, placebo-controlled trial was conducted in accordance with applicable country or local ethical requirements, and all patients provided written informed consent to participate. Fifty centers participated in the study (21 sites in the United States and 29 sites outside the United States).

Patients

The study enrolled cisplatin-naïve patients age ≥ 18 years who had histologically confirmed solid tumors, had a Karnofsky score ≥ 60, and were scheduled to receive a chemotherapy regimen that included cisplatin ≥ 70 mg/m^2. Female patients of childbearing potential were required to have a negative β-human chorionic gonadotropin test result. The primary criteria for exclusion from the study included the following: concomitant treatment with a nonapproved drug within 4 weeks of study entry; significantly abnormal laboratory values (including white blood cell count < 3000/mm^3, absolute neutrophil count < 1500/mm^3,

platelet count $< 100{,}000/mm^3$, aspartate aminotransferase $> 2.5 \times$ upper limit of normal; alanine aminotransferase $> 2.5 \times$ upper limit of normal, bilirubin $> 1.5 \times$ upper limit of normal, or creatinine $> 1.5 \times$ upper limit of normal); known central nervous system malignancy; active infection or uncontrolled disease that, in the opinion of the investigator, should exclude the patient for safety reasons; a planned regimen of multiple-day, cisplatin-based chemotherapy in a single cycle; moderately or highly emetogenic chemotherapy on the days prior to and/or after cisplatin; or radiation therapy to the abdomen or pelvis within 1 week prior to Day 1 of the study. Aside from study drug, additional antiemetics including benzodiazepines, opiates, or other agents (such as 5-HT_3 antagonists, phenothiazines, butyrophenones, benzamides, domperidone, or cannabinoids) were not permitted within 72 hours of Day 1, except as rescue therapy for established nausea or emesis after cisplatin. Corticosteroid therapy equivalent to ≤ 10 mg of prednisone was permitted provided it was not initiated within 72 hours of Day 1.

Procedures

At the beginning of the study, patients who met all entry criteria were assigned to 1 of 3 treatment groups according to a computer-generated randomization schedule. Randomization was stratified by gender and the use of concomitant emetogenic chemotherapy categorized according to the Hesketh classification of emetogenicity.[5] Patients were scheduled to receive a standard therapy regimen, which consisted of intravenous ondansetron 32 mg and oral dexamethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5, plus one of the following three regimens: aprepitant 375 mg on Day 1 and 250 mg on Days 2–5 (aprepitant 375/250 mg); aprepitant 125 mg on Day 1 and 80 mg on Days 2–5 (aprepitant 125/80 mg); or placebo on Days 1–5.

During the study, new data in healthy volunteers became available showing that plasma levels of aprepitant attained by the 375/250-mg regimen were higher than expected and probably were higher than required for attainment of 90% occupancy of central NK_1 receptors, and that the aprepitant 125/80 mg dose most likely would provide full clinical efficacy. In addition, new data also suggested the occurrence of a pharmacokinetic interaction between the aprepitant 375/250-mg regimen and dexamethasone. Therefore, the aprepitant 375/250-mg dose regimen in the current study was discontinued and replaced with an aprepitant 40/25-mg dose regimen, and a new randomization schedule was generated after the dose-group adjustment. Enrollment into the aprepitant 125/80-mg group and the standard therapy group continued under the original randomization schedule until the new schedule became available. The primary efficacy analyses in this report are based on patients who were randomized with the new randomization schedule. The safety analyses are based on data from all patients both before and after the dose-group adjustment.

One hour prior to cisplatin infusion, patients received either aprepitant 375 mg, aprepitant 125 mg, aprepitant 40 mg, or placebo. Thirty minutes prior to cisplatin infusion, all patients received intravenous ondansetron and oral dexamethasone. Cisplatin ≥ 70 mg/m^2 was infused over a period of ≤ 3 hours, with the start of infusion designated as T_{zero} (hours). Patients who received docetaxel or paclitaxel in addition to cisplatin were given dexamethasone 20 mg 12 hours and 6 hours prior to paclitaxel or docetaxel infusion, followed by aprepitant or placebo 1 hour prior to cisplatin infusion, and ondansetron 30 minutes prior to cisplatin infusion.

Every morning between 8 AM and 10 AM on Days 2–5, patients took a capsule formulation of either aprepitant or placebo. In addition, all patients received oral dexamethasone 8 mg. Patients returned to the clinic for a poststudy visit between 1 day and 3 days after the last dose of study medication and again between Days 19–29 postcisplatin for follow-up examination and laboratory tests. Completion of the study was defined as completion of the Day 19–29 visit, and cessation of the study at any other time was considered a discontinuation.

Assessments

Patients maintained a diary throughout the study, beginning on Day 1. Efficacy assessments began just prior to cisplatin infusion and continued for a total of 5 days. Patients recorded the date and time of episodes of vomiting (expulsion of stomach contents through the mouth) or retching (an attempt to vomit that was not productive of stomach contents), with distinct episodes defined as those separated by at least 1 minute. The use of rescue medication, including drug, dose, and time, also was recorded. Nausea was assessed by the patient using a 100-mm, horizontal visual analogue scale (VAS) that asked how much nausea the patient had over the last 24 hours, with 0 mm labeled *no nausea* and 100 mm labeled *nausea as bad as it could be*. Every day between 8 AM and 10 AM, patients placed a vertical mark on the scale corresponding to the degree of nausea they experienced in the preceding 24 hours. On Days 2–5, daily telephone contact was made by study site personnel to confirm that patients were taking study medications appropri-

ately and were maintaining accurate records of dosing times, treatment response, any adverse events, and use of rescue medication. The diary was reviewed with the patient at the Day 6–8 clinic visit. Tolerability was monitored by physical examinations, including vital signs and weight measurement, laboratory studies, and electrocardiograms, as well as by adverse events. Baseline safety assessments were obtained at the prestudy visit, and vital signs and electrocardiograms were monitored on the day of treatment. Physical and laboratory tests were repeated at the Day 6–8 clinic visit and again when patients returned for the Day 19–29 follow-up visit, or at discontinuation.

Statistical Analysis

The primary endpoint of the efficacy analysis was the proportion of patients who achieved a complete response, which was defined as no emetic episodes and no rescue therapy, on Days 1–5 (overall study period). The primary efficacy analysis focused on data obtained from that portion of the study in which patients were randomized to receive the aprepitant 125/80-mg regimen, the aprepitant 40/25-mg regimen, or standard therapy, because the dose-response relationships of main interest were among those groups.

In addition, secondary endpoints were assessed as the proportions of patients who achieved a response to treatment in the following categories: 1) no emesis, 2) no rescue therapy, 3) no nausea (maximum VAS < 5 mm), 4) no significant nausea (maximum VAS < 25 mm), and 5) total control (no emetic episodes, no use of rescue therapy, and maximum nausea VAS < 5 mm). Time to first emesis, total number of emetic episodes, and complete protection (defined as no emetic episodes, no rescue, and maximum nausea VAS < 25 mm) were evaluated as exploratory endpoints.

All analyses were performed using an intent-to-treat approach. To be considered evaluable for this efficacy analysis, a patient had to have received cisplatin-based chemotherapy and at least one dose of study drug, and had to have recorded at least one posttreatment efficacy assessment. 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). Treatment comparisons were made using logistic regression models, which included terms for treatment, gender, use of concomitant chemotherapy, and region (United States vs. non-United States). In addition, the primary efficacy variable was examined by age group (< 65 years vs. ≥ 65 years and < 75 years vs. ≥ 75 years) and race. Logistic regression analyses were performed to examine the effect of dose on complete response. Standard therapy was included in one of these analyses. In addition, an exploratory analysis was performed to examine the total number of emetic episodes (0, 1–2, or ≥ 3) for the aprepitant 125/80-mg group, the aprepitant 40/25-mg group, and the standard therapy group.

A 20-percentage point difference was anticipated between the aprepitant 125/80-mg dose group versus the standard therapy group with respect to the primary endpoint of complete response. Based on a sample size of 100 patients per group, the study had 79% power to detect this difference based on a two-sided test with a significance level $\alpha = 0.05$. A step-down procedure was used to adjust for the multiplicity of having two comparisons for the primary endpoint, but no multiplicity adjustments were made for the secondary comparisons, for which nominal P values are reported.

For thoroughness, an additional comparison was made between aprepitant 125/80 mg and standard therapy using all available data, including the data obtained before the dose adjustment was made. For the overall study period, a logistic regression model was used to test for interaction between the 2 parts of the study (i.e., before and after the dose groups were adjusted) to assess the validity of combining the data from the 2 separate randomization schedules. Because the P value of the test was not statistically significant ($P = 0.185$), it was concluded that there was no treatment-by-part interaction and, thus, the data in question could be pooled.

Statistical analyses for tolerability were performed using all available data. Safety data were analyzed using tabulations of adverse events and protocol-specified laboratory parameters for all patients who received at least 1 dose of study medication. Treatment comparisons of the aprepitant 125/80-mg regimen versus the standard therapy regimen were performed with respect to the patient incidence of 1) at least one adverse event, 2) a drug-related adverse event (i.e., an adverse event that the investigator determined was possibly, probably, or definitely related to study drug), 3) a serious adverse event (according to a standard regulatory definition), and 4) discontinued treatment due to an adverse event. Comparisons also were performed for the incidence of febrile neutropenia, in part because of its predictable occurrence in a subset of patients receiving high-dose cisplatin and also to account for the possibility that its frequency may have been increased if the toxicity of either chemotherapy or dexamethasone were enhanced by aprepitant. Tests of significance were performed for these 5 endpoints, and the corresponding relative risk and P values were provided (with P value ≤ 0.05 considered significant).

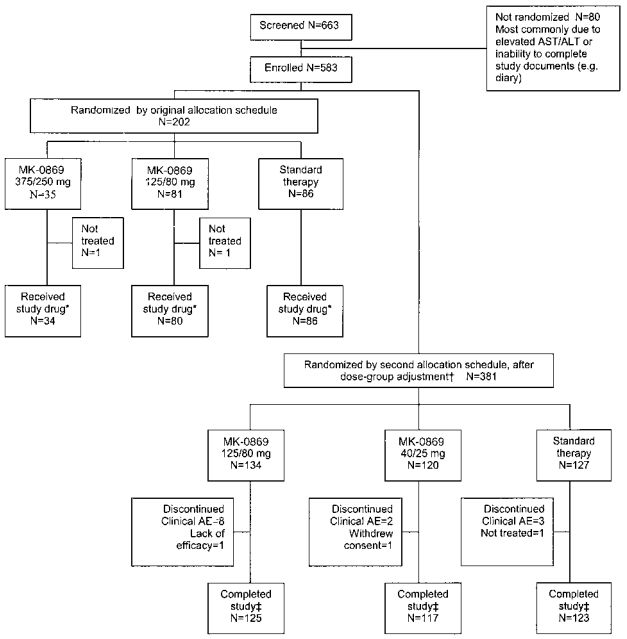

FIGURE 1. Study flow chart. The aprepitant 375/250 mg group received standard therapy plus aprepitant 375 mg on Day 1 and aprepitant 250 mg on Days 2–5; the aprepitant 125/80 mg group received standard therapy plus aprepitant 125 mg on Day 1 and aprepitant 80 mg on Days 2–5; and the aprepitant 40/25 mg group received standard therapy plus aprepitant 40 mg on Day 1 and aprepitant 25 mg on Days 2–5. Standard therapy consisted of intravenous ondansetron 32 mg plus oral dexmethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5. Asterisks indicate groups that were included only in the tolerability analyses, a single dagger indicates groups that were included in the primary efficacy and tolerability analyses, and double daggers indicate groups that completed the Day 19–29 follow-up visit. AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

RESULTS

Patients

Figure 1 shows the disposition of patients throughout the study. A total of 663 patients were screened, and 80 of those patients were not randomized, mostly due to elevated aspartate aminotransferase or alanine aminotransferase levels or an inability to understand or complete the required study documents. Of the 583 patients who were enrolled in the study, 580 patients received at least 1 dose of study drug and were included in the tolerability analyses. Of these, 381 patients enrolled after the dose group adjustment; the primary efficacy analysis focused on the 377 evaluable patients from this subset.

The characteristics of the 381 randomized patients are shown in Table 1. The 3 treatment groups included in the primary efficacy analysis were similar with respect to age, gender, race, alcohol intake, and use of other highly emetogenic chemotherapy. The mean dose of cisplatin, use of additional chemotherapeutic agents (including highly emetogenic chemotherapy), use of concomitant medications, and use of rescue medications were similar across treatment groups, as were the primary cancer diagnoses (Table 1) and secondary diagnoses (not shown).

Efficacy

The proportion of patients who achieved a complete response in the overall study period was significantly higher in both aprepitant groups compared with the standard therapy group (71.0% in the aprepitant 125/80-mg group, 58.8% in the aprepitant 40/25-mg group, and 43.7% in the standard therapy group; $P < 0.01$ for aprepitant 125/80 mg vs. standard therapy; $P < 0.05$ for aprepitant 40/25 mg vs. standard therapy) (Fig. 2). A small number of patients ($n = 34$) enrolled in the aprepitant 375/250-mg dose group before the dose-group adjustment; the proportion of patients in this group who achieved a complete response in the overall study period (70%) was similar to the proportion of patients in the aprepitant 125/80-mg group.

Figure 3 shows results of the complete response comparisons for the acute and delayed phases. During the acute phase (Day 1), a significantly greater proportion of patients achieved a complete response in the aprepitant 125/80-mg group (83.2%) compared with the standard therapy group (71.4%; $P = 0.014$). In the aprepitant 40/25-mg group, 75.6% of patients had a complete response. In the delayed phase (Days 2–5), the complete response rates for both aprepitant groups were significantly greater compared with the rate for the standard therapy group (72.7% for aprepitant 125/80 mg, 63.9% for aprepitant 40/25 mg, and 45.2% for standard therapy; $P < 0.001$ for aprepitant 125/80 mg vs. standard therapy; $P = 0.002$ for aprepitant 40/25 mg vs. standard therapy). When interaction of study factors (e.g., gender, region, and use of concomitant chemotherapy) and treatment group was assessed, no interactions were found to be statistically significant ($P \geq 0.306$ for all interactions). Similar to the overall study period, the aprepitant 375/250-mg dose group achieved results similar to those achieved in the aprepitant 125/80-mg group: the percentages of patients who achieved a complete response in the acute phase and the delayed phase were 91% and 73%, respectively.

The results of treatment comparisons for additional efficacy endpoints in the acute phase, the delayed phase, and the overall study period are shown in Table 2. In the acute phase, the aprepitant 125/80-mg regimen was superior to standard therapy for no emesis ($P < 0.01$) and for complete protection ($P < 0.05$); however, the treatment groups did not differ signifi-

TABLE 1
Patient Baseline Characteristics by Treatment Group[a]

Characteristic	A 125/80 mg plus standard therapy (n = 134 patients)	A 40/25 mg plus standard therapy (n = 120 patients)	Standard therapy (n = 127 patients)
Female (%)	45.5	42.5	42.5
Age (mean yrs ± SD)	56.0 ± 13.0	58.4 ± 13.4	53.7 ± 13.2
Race (%)			
White	58.2	60.0	56.7
Black	5.2	6.7	7.1
Other	36.6	33.3	36.2
Alcohol intake (drinks per week) (%)			
0	72.4	77.5	74.0
1–10	20.9	15.8	21.2
>10	6.7	5.8	4.7
Receiving concurrent emetogenic chemotherapy (Hesketh level ≥ 3) (%)	19.4	17.5	17.3
Mean cisplatin dose (mg/m^2)	79.9	81.2	82.7
Primary cancer diagnosis			
Respiratory	44.0	44.2	42.5
Urogenital	26.9	25.8	28.3
Other	28.9	29.2	28.4

SD: Standard deviation; A 125/80 mg: standard therapy plus aprepitant 125 mg on Day 1 and 80 mg on Days 2–5; A 40/25 mg: standard therapy plus aprepitant 40 mg on Day 1 and 25 mg on Days 2–5; standard therapy: intravenous ondansetron 32 mg plus oral dexmethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5.

[a] Data shown were obtained after the dose adjustment.

cantly with regard to any other endpoints in the acute phase. In the delayed phase, the aprepitant 125/80-mg regimen was superior to standard therapy ($P < 0.01$) in all endpoint comparisons, and the aprepitant 40/25-mg regimen was superior to standard therapy ($P < 0.05$) in all but one endpoint (no significant nausea). Similarly, for the overall study period, the aprepitant 125/80-mg regimen was superior to standard therapy ($P < 0.01$) in all endpoint comparisons, whereas the aprepitant 40/25-mg regimen was superior ($P < 0.05$) in only 4 of the 6 additional endpoints.

In an analysis of dose response that included aprepitant 125/80 mg, aprepitant 40/25 mg, and standard therapy, dose was a statistically significant positive predictor of complete response ($P < 0.001$). In the analysis that did not include standard therapy, the difference between the aprepitant 125/80-mg regimen and the aprepitant 40/25-mg regimen also was significant ($P = 0.035$).

In the overall study period, fewer emetic episodes occurred in the aprepitant groups compared with the standard therapy group. In the aprepitant 125/80-mg group, 12.2% of patients had ≥ 3 emetic episodes compared with 23.5% in the aprepitant 40/25-mg group and 36.5% in the standard therapy group ($P < 0.001$ in a post-hoc comparison of aprepitant 125/80 mg vs. standard therapy). Furthermore, among the patients who had vomiting, a lower frequency of

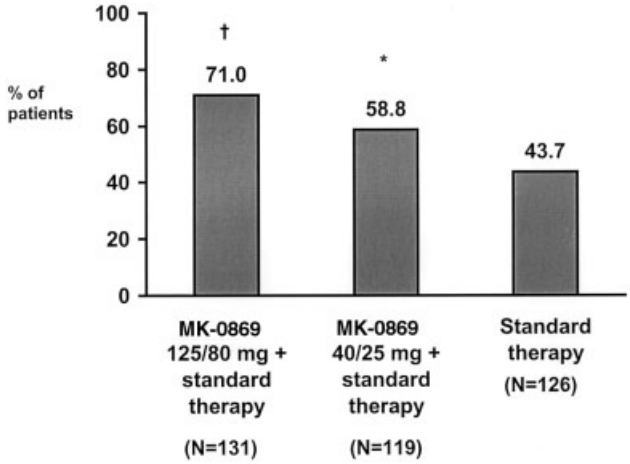

FIGURE 2. Percentages of patients who achieved a complete response (no emesis and no rescue therapy) in the overall study period (Days 1–5). The aprepitant 125/80 mg group received standard therapy plus aprepitant 125 mg on Day 1 and 80 mg on Days 2–5 ($P < 0.01$ vs. standard therapy; dagger), and the aprepitant 40/25 mg group received standard therapy plus aprepitant 40 mg on Day 1 and 25 mg on Days 2–5 ($P < 0.05$ vs. standard therapy; asterisk). Standard therapy consisted of intravenous ondansetron 32 mg plus oral dexamethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5. The data shown were obtained after the dose adjustment.

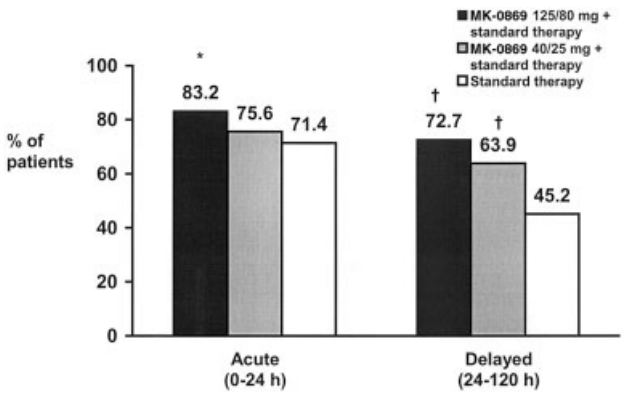

FIGURE 3. Percentages of patients who achieved a complete response (no emesis and no rescue therapy) in the acute phase (Day 1) and in the delayed phase (Days 2–5). The aprepitant 125/80 mg group (n = 131 patients in the acute phase and n = 132 patients in the delayed phase) received standard therapy plus aprepitant 125 mg on Day 1 and 80 mg on Days 2–5; the aprepitant 40/25 mg group (n = 119 patients) received standard therapy plus aprepitant 40 mg on Day 1 and 25 mg on Days 2–5. Standard therapy (n = 126 patients) consisted of intravenous ondansetron 32 mg plus dexamethasone 20 mg on Day 1 and dexamethasone 8 mg on Days 2–5. The asterisk indicates $P < 0.05$ versus standard therapy, and daggers indicate $P < 0.01$ versus standard therapy. The data shown were obtained after the dose adjustment.

emetic episodes was noted for the aprepitant 125/80-mg regimen (11.5% of patients had 1–2 episodes, and 12.2% of patients had ≥ 3 episodes; n = 131 patients) compared with the aprepitant 40/25-mg regimen (10.9% of patients had 1–2 episodes, and 23.5% of patient had ≥ 3 episodes; n = 119 patients) or standard therapy (15.1% of patients had 1–2 episodes, and 36.5% of patients had ≥ 3 episodes; n = 126 patients).

Figure 4 shows the comparison of complete response rates with aprepitant 125/80 mg versus standard therapy using data combined from both randomization periods (before and after the dose adjustment). The percentage of patients who achieved a complete response was significantly greater in the aprepitant 125/80-mg group (n = 211 patients) compared with the standard therapy group (n = 210 patients) for the overall study period (68.2% vs. 45.7%, respectively), the acute phase (84.4% vs. 71.9%, respectively), and the delayed phase (71.2% vs. 46.7%, respectively; $P < 0.001$ for all 3 comparisons).

Tolerability

Of the 583 randomized patients, all 580 patients who received study therapy were included in the tolerability analyses. Thirty-four patients received the aprepitant 375/250-mg dose before the regimen was discontinued due to the newly obtained pharmacokinetic data, 214 patients received the aprepitant 125/80-mg dose, 120 patients received the aprepitant 40/25-mg dose once it was added to the study, and 212 patients received standard therapy. Table 3 summarizes adverse events reported up to 14 days after treatment. A total of 428 patients (73.7%) had clinical adverse events. The aprepitant 125/80-mg group had the highest rates of adverse events, drug-related adverse events, and discontinuations due to serious adverse events, although the relative risks in the aprepitant 125/80-mg group compared with the standard therapy group for these categories were not statistically significant (adverse events: relative risk, 1.06; P = 0.448; drug-related adverse events: relative risk, 1.05; P = 0.831; discontinuations due to serious adverse events: relative risk, 1.32; P = 0.804).

Serious clinical adverse events (designated by the investigator according to a regulatory definition specified by the protocol) were more frequent in the aprepitant groups versus the standard therapy group (20.6% in the aprepitant 375/250-mg group, 21.5% in the aprepitant 125/80-mg group, 16.7% in the 40/25-mg group, and 12.3% in the standard therapy group), and the relative risk of a serious adverse event in the aprepitant 125/80-mg group compared with the standard therapy group was 1.75 (P = 0.032). Of 11 patients who died during the study, all had completed the full 5 days of study therapy. One patient was in the aprepitant 375/250-mg group, 8 patients were in the aprepitant 125/80-mg group, and 2 patients were in the standard therapy group. For the 8 patients in the aprepitant 125/80-mg group, the causes of death included hepatic failure due to hepatic tumor, pulmonary emboli, hemorrhage, cardiac arrest, pneumonia, and respiratory insufficiency. The range of causes of death among treatment groups was consistent with expectations for a patient population with cancer receiving chemotherapy based on high-dose cisplatin.

A difference in the relative frequency of infection-related serious adverse events, defined as either documented infections or reports of febrile neutropenia, was observed between the aprepitant 125/80-mg group and the standard therapy group. Specifically, 28 patients (13%) in the aprepitant 125/80-mg group had serious infection-related adverse events, compared with 9 patients (4.2%) in the standard therapy group. The incidence of other serious adverse events was generally similar across treatment groups. One patient in the aprepitant 40/25-mg group developed Stevens–Johnson syndrome, which the investigator considered drug-related. Stevens–Johnson syndrome has been reported in a patient receiving cisplatin and also has been noted more frequently in patients who are treated with corticosteroids. This patient was also tak-

TABLE 2
Percentages of Patients Reaching Efficacy Endpoints, by Study Phase and Treatment Group, Using Data Obtained after the Dose Adjustment

	Treatment group								
	Acute phase (0–24 hours)			Delayed phase (24–120 hours)			Overall (0–120 hours)		
Endpoint	A 125/80	A 40/25	ST	A 125/80	A 40/25	ST	A 125/80	A 40/25	ST
Total no.	131	119	126	132	119	126	131	119	126
No emesis (%)	87.0[a]	80.7	73	77.3[a]	69.7[a]	50.0	76.3[a]	65.5[a]	48.4
No rescue (%)	93.9	87.4	93.7	85.6[a]	75.6[b]	63.5	83.2[a]	73.1	63.5
No nausea (%)	71.8	70.6	66.7	58.3[a]	52.9[a]	36.5	52.7[a]	48.7[b]	34.1
No significant nausea (%)	90.8	86.6	87.3	83.3[a]	68.9	62.7	81.7[a]	68.9	58.7
Complete protection (%)	79.4[b]	72.3	66.7	67.4[a]	58.0[a]	41.3	64.9[a]	53.8[b]	39.7
Total control (%)	67.9	63.0	58.7	51.5[a]	51.3[a]	32.5	47.3[a]	44.5[b]	31.0

A 125/80: standard therapy plus aprepitant 125 mg on Day 1 and aprepitant 80 mg on Days 2–5; A 40/25: standard therapy plus aprepitant 40 mg on Day 1 and 25 mg on Days 2–5: ST; standard therapy (intravenous ondansetron 32 mg plus oral dexamethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5; No nausea: visual analogue scale (VAS) score <5 mm; No significant nausea: VAS score <25 mm; 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).

[a] $P < 0.01$ versus standard therapy.

[b] $P < 0.05$ versus standard therapy.

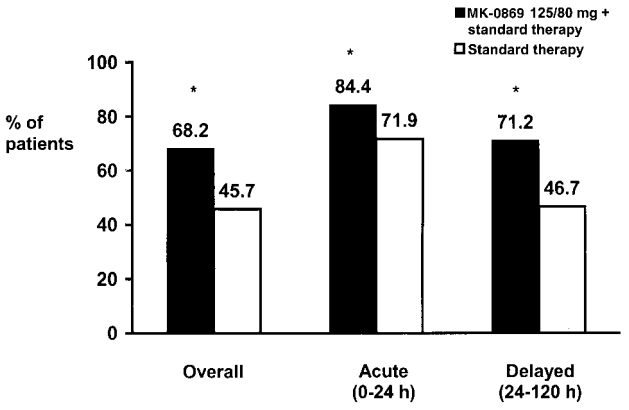

FIGURE 4. Percentages of all patients who received aprepitant 125/80 mg (standard therapy plus aprepitant 125 mg on Day 1 and 80 mg on Days 2–5; $n = 211$ patients in the overall study period and the acute phase; $n = 212$ in the delayed phase) or standard therapy alone (intravenous ondansetron 32 mg plus oral dexmethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5) ($n = 210$) and achieved a complete response in the overall study period, the acute phase, and the delayed phase (data were combined from before and after the dose adjustment). Asterisks indicate $P < 0.001$ versus standard therapy.

ing tramadol, which has been associated with Stevens–Johnson syndrome, and the patient received 5-fluorouracil, which has been associated with erythema multiforme.[18–21]

The most common adverse events (≥ 10% of patients in at least one treatment group) were fatigue, constipation, diarrhea, nausea, neutropenia, anorexia, headache, and hiccups (Table 3). Although there were higher incidences of fatigue, hiccups, and the syndrome of febrile neutropenia in the aprepitant 125/80-mg group compared with the standard therapy group, there was no evidence of a clear dose-response relation for these adverse events. The increase in risk for febrile neutropenia (serious or nonserious) in the aprepitant 125/80-mg group compared with the standard therapy group was not significant in a prespecified analysis ($P = 0.459$). The incidence of headache was similar across treatment groups, and incidences of constipation and diarrhea were similar between the aprepitant 125-mg group and the standard therapy group. The treatment groups were similar for use of growth factors and for clinical adverse events typically associated with toxic effects of chemotherapy, including mucositis, stomatitis, or pharyngitis.

Of the 580 patients who received study therapy, 131 patients (22.6%) had ≥ 1 laboratory adverse events, none of which was serious; no patients died or discontinued due to laboratory adverse events. The frequency of laboratory adverse events was similar across all treatment groups. Drug-related laboratory adverse events were most frequent in the standard therapy group (8.5%). The pattern of National Cancer Institute (NCI) toxicity Grade 3 or Grade 4 decreases in hematologic laboratory values measured at the Day 19–29 posttreatment visit generally was similar across treatment groups. No patient in any treatment group had an NCI toxicity Grade 3 or Grade 4 elevation in liver function tests (alanine aminotransferase or aspartate aminotransferase) at the Day 19–29 visit, and the pattern of NCI toxicity Grade 3 or Grade 4 elevations in serum creatinine also was similar across treatment groups:

TABLE 3
Summary of Adverse Events

Percent of patients	Percent of patients			
	A 375/250 mg plus standard therapy (n = 34 patients)	A 125/80 mg plus standard therapy (n = 214 patients)	A 40/25 mg plus standard therapy (n = 120 patients)	Standard therapy (n = 212 patients)
With ≥1 adverse event	85	76	71	72
With drug-related adverse events[a]	15	27	27	26
With serious adverse events	21	22	17	12
Discontinued due to adverse events	9	2	1	1
With ≥1 laboratory adverse event	27	23	22	22
With drug-related laboratory adverse events	0	8	6	9
With most common adverse events[b]				
Asthenia/fatigue	21	20	13	17
Constipation	15	14	12	13
Diarrhea	12	11	11	12
Nausea	21	13	12	11
Neutropenia	12	3	2	6
Anorexia	0	12	6	11
Headache	9	8	8	10
Hiccups	9	12	16	9
With febrile neutropenia	6	6	8	4

A 375/250 mg: standard therapy plus aprepitant 375 mg Day 1 and 250 mg on Days 2–5; A 125/80: standard therapy plus aprepitant 125 mg on Day 1 and 80 mg on Days 2–5; A 40/25: standard therapy plus aprepitant 40 mg on Day 1 and 25 mg on Days 2–5; standard therapy: intravenous ondansetron 32 mg plus oral dexamethasone 20 mg on Day 1 and oral dexamethasone 8 mg on Days 2–5.

[a] Determined by the investigator as possibly drug related, probably drug related, or definitely drug related.

[b] Incidence ≥10% in at least one treatment group.

2 patients (1%) in the aprepitant 125/80 mg group and no patients in all other groups.

DISCUSSION

The patient population in this study was typical of that evaluated in previous antiemetic studies of aprepitant and other antiemetics, such as the 5-HT_3 RAs.[14,15,22] Patients in each treatment group received comparable chemotherapy regimens. Because patients could take rescue therapy for treatment of emesis and/or nausea, the primary endpoint of complete response (no emesis and no use of rescue therapy) not only reflected prevention of emesis but also functioned as a surrogate index of nausea control: patients were classified as treatment failures either if they had vomiting or if they took rescue therapy for nausea. In the assessment of complete response for the overall study period, treatment with aprepitant 125/80 mg or 40/25 mg plus standard therapy was significantly more effective compared with standard therapy alone. In addition, for all other endpoints assessed (no vomiting, no rescue, no nausea, no significant nausea, total control, and complete protection) in the overall study period, aprepitant 125/80 mg plus standard therapy was statistically superior to standard therapy alone, with between-treatment differences exceeding 10 percentage points (the minimum generally considered clinically meaningful).[14]

The superior efficacy of the aprepitant 125/80-mg regimen was demonstrated further when the acute and delayed phases were assessed separately. During the acute phase (Day 1), the superiority of the aprepitant 125/80-mg regimen, compared with standard therapy, was significant for the endpoints of complete response, complete protection, and no emesis. The superiority of the aprepitant 125/80-mg regimen, compared with standard therapy, was particularly robust during the delayed phase (Days 2–5), in which treatment differences were both statistically and clinically significant for every endpoint. Differences between the aprepitant 40/25-mg regimen and standard therapy were seen less consistently compared with the aprepitant 125/80-mg regimen. Efficacy findings for the aprepitant 375/250-mg dose, although they were based on a small number of patients, were very similar to findings for the aprepitant 125/80-mg dose for all three intervals assessed (overall, acute, and delayed phases), suggesting that the aprepitant 375/250-mg regimen would not provide added benefit over the aprepitant 125/80-mg regimen.

In the dose-response analysis which included aprepitant 125/80 mg, aprepitant 40/25 mg, and stan-

dard therapy, it was observed that dose was a significant positive predictor of complete response; within this analysis, a significant difference also was noted between the 2 aprepitant groups. Likewise, in the second dose-response analysis, which compared aprepitant 125/80 mg with aprepitant 40/25 mg and excluded standard therapy, dose was again associated positively with complete response, indicating that the significance of dose as a positive predictor of complete response was not entirely attributable to comparisons with standard therapy. Moreover, the proportion of patients who had multiple emetic episodes was lowest in the aprepitant 125/80-mg group; and, among all patients who did have emesis, episodes were less frequent for patients in the aprepitant 125/80-mg group compared with patients in the aprepitant 40/25-mg group or the standard therapy group. To take into consideration all available data for the aprepitant 125/80-mg group and the standard therapy group, an additional analysis was performed comparing efficacy results from all patients in these treatment groups, irrespective of randomization schedule. Results of this pooled analysis showed that aprepitant 125/80 mg was superior to standard therapy in all 3 study periods (overall, acute, and delayed), consistent with the results of the primary efficacy comparisons.

Tolerability assessments, which were performed using data pooled from before and after the dose adjustment, showed that in general, the adverse event profile of the patients in this study was typical for a population of patients with cancer receiving chemotherapy based on high-dose cisplatin. The overall incidence of adverse events (clinical, laboratory, and other) was generally similar across treatment groups. There were more deaths in the aprepitant 125/80-mg treatment group compared with the standard therapy group, although the spectrum of causes of death was not suggestive of an association with aprepitant administration. There also was a greater number of patients who had serious adverse events in the aprepitant 125/80-mg treatment group compared with the standard therapy group, a consequence of the greater number of infection-related adverse events reported in the aprepitant 125/80-mg treatment group.

Several potential explanations for the increased incidence of infection-related serious adverse events and febrile neutropenia were evaluated. There did not appear to be an increased incidence of direct hematologic toxicity associated with aprepitant administration. Specifically, no consistent pattern of increased incidence of neutropenia, thrombocytopenia, or anemia was observed in association with aprepitant. Although the timing of the protocol-specified laboratory analyses was not optimal for detection of the predictable chemotherapy-induced nadirs in hematologic indices, the analyses done after Day 5 presumably would detect abnormalities of unusual severity and/or duration. The hematologic safety profile therefore did not suggest that aprepitant caused direct hematologic toxicity. Similarly, subgroup analyses did not reveal an association between concomitant chemotherapy known to be metabolized by CYP-3A4 and an increased incidence of serious adverse events in general or febrile neutropenia or infection in particular. Mucositis-related adverse events (mucous membrane disorder, stomatitis, and pharyngitis) were not consistently more frequent in the aprepitant treatment groups, and no increased use of growth factors was seen in patients who received aprepitant compared with patients who did not, all of which suggests that the toxicity of chemotherapy was not augmented by aprepitant.

Another possible explanation for the increased incidence of febrile neutropenia and infections seen in the aprepitant 125/80-mg group involves dexamethasone. Corticosteroids have been associated with increased susceptibility to infection when administered in high doses.[23–26] Because of a pharmacokinetic interaction in which aprepitant has been shown to increase plasma dexamethasone levels greater than twofold, it is possible that increased exposure to dexamethasone may have contributed to the increased incidence of febrile neutropenia and infection seen in the aprepitant groups in the current study, although no clear evidence of a dose-response relationship was noted. It is noteworthy that in prior clinical studies of aprepitant for the prevention of CINV, no increase was observed in infection-related adverse events associated with aprepitant.[14–17] In those studies, dexamethasone was coadministered only for 1 day. In 2 recently conducted Phase III trials that used a modified dexamethasone regimen to produce more closely matched dexamethasone levels in patients who received aprepitant versus patients who received only standard therapy, no differential incidence of serious infections or febrile neutropenia was seen (data on file). Whether this altered corticosteroid dosing schedule or other patient or treatment factors led to the lower observed toxicity cannot be determined definitively from these analyses.

In summary, both the aprepitant 125/80-mg regimen and the aprepitant 40/25-mg regimen were consistently more effective than standard therapy alone, and the aprepitant 125/80-mg regimen provided greater benefit compared with the aprepitant 40/25-mg regimen. Even in patients who did have breakthrough emesis, the aprepitant 125/80-mg regimen appeared to reduce the frequency of multiple emetic

events. Because the interaction of dexamethasone with aprepitant documented in a pharmacokinetic study resulted in elevated dexamethasone levels, it may be asked whether the superior efficacy of the aprepitant regimens in the current study may have been due in part to dexamethasone rather than to an effect solely of aprepitant. Although this possibility cannot be excluded definitively, the degree of antiemetic protection observed in this study was much greater compared to that reported previously with dexamethasone alone.[6] Although more serious adverse events related to infection were associated with aprepitant compared with standard therapy, aprepitant was generally well tolerated. Therefore, in the context of both efficacy and tolerability findings, the aprepitant 125/80-mg dose was determined to be the most appropriate for further clinical study.

REFERENCES

1. Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT3 receptor antagonists. *Support Care Cancer.* 1994;2:286–292.
2. de Boer-Dennert M, de Wit R, Schmitz PIM, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5-HT3 antagonists. *Br J Cancer.* 1997;76:1055–1061.
3. Griffin AM, Butow PN, Coates AS, et al. On the receiving end V: patient perceptions of the side effects of cancer chemotherapy in 1993. *Ann Oncol.* 1996;7:189–195.
4. Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *N Engl J Med.* 1993; 329:1790–1796.
5. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol.* 1997;15:103–109.
6. Tavorath R, Hesketh PJ. Drug treatment of chemotherapy-induced delayed emesis. *Drugs.* 1996;52:639–648.
7. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin Oncol.* 1999;17:2971–2994.
8. Watson JW, Gonsalves SF, Fossa AA, et al. The anti-emetic effects of CP-99,994 in the ferret and the dog: role of the NK1 receptor. *Br J Pharmacol.* 1995;115:84–94.
9. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. *Physiol Rev.* 1993;73:229–308.
10. Diemunsch P, Grélot L. Potential of substance P antagonists as antiemetics. *Drugs.* 2000;60:533–546.
11. Bountra C, Bunce K, Dale T, et al. Anti-emetic profile of a non-peptide neurokinin NK1 receptor antagonist, CP-99,994 in ferrets. *Eur J Pharmacol.* 1993;249:R3–R4.
12. Tattersall FD, Rycroft W, Hill RG, Hargreaves RJ. The tachykinin NK_1 receptor antagonist CP-99,994 attenuates cisplatin-induced emesis in the ferret. *Eur J Pharmacol.* 1993;250: R5–R6.
13. Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK_1 receptor antagonist aprepitant (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. *Neuropharmacology.* 2000;39:652–663.
14. Cocquyt V, Van Belle S, Reinhardt RR, et al. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. *Eur J Cancer.* 2001;37:835–842.
15. Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol.* 2001;19:1759–1767.
16. Van Belle S, Lichinitser M, Navari R, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869: a randomized controlled trial. *Cancer.* 2002;94:3032–3041.
17. Navari R, Reinhardt R, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1 receptor antagonist. *N Engl J Med.* 1999;340:190–195.
18. Ortho-McNeil Pharmaceutical. Product information. ULTRAM®. U.S. package insert. Raritan, NJ: Ortho-McNeil Pharmaceutical, 2001.
19. Lo SK, Yip D, Leslie M, Harper P. 5-fluorouracil-induced erythema multiforme. *Int J Clin Pract.* 1999;53:219–221.
20. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333:1600–1607.
21. Brodsky A, Aparici I, Argeri C, Goldenberg D. Stevens–Johnson syndrome, respiratory distress and acute renal failure due to synergic bleomycin-cisplatin toxicity. *J Clin Pharmacol.* 1989;29:821–823.
22. Olver I, Paska W, Depierre A, et al. A multicenter, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. *Ann Oncol.* 1996;7:945–952.
23. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis.* 1989;11:954–963.
24. De La Rosa GR, Champlin RE, Kontoyiannis DP. Risk factors for the development of invasive fungal infections in allogeneic blood and marrow transplant recipients. *Transplant Infect Dis.* 2002;4:3–9.
25. DeMaria EJ, Reichman W, Kenney PR, Armitage JM, Gann DS. Septic complications of corticosteroid administration after central nervous system trauma. *Ann Surg.* 1985;207: 248–252.
26. Gerndt SJ, Rodriguez JL, Pawlik JW, et al. Consequences of high-dose steroid therapy for acute spinal cord injury. *J Trauma Injury Infect Crit Care.* 1997;42:279–284.