

Prevention of Cisplatin-Induced Emesis by the Oral Neurokinin-1 Antagonist, MK-869, in Combination With Granisetron and Dexamethasone or With Dexamethasone Alone

By Daniel Campos, Jose Rodrigues Pereira, Rick R. Reinhardt, Carlos Carracedo, Sergio Poli, Conrado Vogel, Jorge Martinez-Cedillo, Aura Erazo, Johanna Wittreich, Lars-Olof Eriksson, Alexandra D. Carides, and Barry J. Gertz

Purpose: The NK1-receptor antagonist MK-869 (L-754,030) has demonstrated antiemetic activity in humans receiving chemotherapy. Objectives of the present trial included the first assessment of oral MK-869 plus dexamethasone compared with a 5HT₃ antagonist plus dexamethasone for prevention of acute and delayed emesis after high-dose cisplatin. Furthermore, the study sought to confirm that addition of MK-869 to a 5HT₃ antagonist plus dexamethasone was more effective than just the 5HT₃ antagonist plus dexamethasone for prevention of acute and delayed emesis.

Patients and Methods: This multicenter, double-blind, parallel-group trial in 351 cisplatin-naïve patients evaluated prevention of acute (0 to 24 hours) and delayed emesis (primary efficacy parameter; days 2 to 5) after cisplatin (≥ 70 mg/m²). Patients were randomized to four groups (I to IV) (n = number randomized; number evaluable): granisetron (10 μ g/kg intravenously) pre-cisplatin followed by placebo on days 2 to 5 (group I) (n = 90; 90); granisetron and MK-869 (400 mg PO [by mouth]) pre-cisplatin, followed by MK-869 (300 mg PO) on days 2 to 5 (group II) (n = 86; 84); MK-869 (400 mg PO) the evening before and pre-cisplatin, followed by MK-869 (300 mg PO) on days 2 to 5 (group III) (n = 89; 88); or MK-869 (400 mg PO) pre-cisplatin, followed by MK-869 (300 mg PO) on days 2 to 5 (group

IV) (n = 86; 84). All patients also received dexamethasone (20 mg PO) before cisplatin. Additional medication was available to treat emesis or nausea at any time.

Results: In the acute period, 57%, 80%, 46%, and 43% of patients were without emesis in groups I, II, III, and IV, respectively ($P < .01$ for group II v group I). In the delayed period, the proportion of patients without emesis in groups I, II, III, and IV was 29%, 63%, 51%, and 57%, respectively ($P < .01$ for groups II, III, and IV v group I). The distribution of nausea scores in the delayed period was lower when comparing group II with group I ($P < .05$ for days 1 to 5 and days 2 to 5). One serious adverse event (dizziness) was rated as possibly related to MK-869.

Conclusion: Once daily oral administration of MK-869 was effective in reducing delayed emesis and nausea after high-dose cisplatin. However, the combination of the 5HT₃ antagonist plus dexamethasone was numerically superior to MK-869 plus dexamethasone in reducing acute emesis. Confirming and extending previous findings, the triple combination of a 5HT₃ antagonist, MK-869, and dexamethasone provided the best control of acute emesis.

J Clin Oncol 19:1759-1767. © 2001 by American Society of Clinical Oncology.

VOMITING AND nausea after administration of anticancer drugs impairs quality of life¹ and are among the most distressing aspects of treatment.² Patients may even delay or refuse further therapy because of severe chemotherapy-induced emesis.³

The severity and pattern of chemotherapy-induced emesis depends on the specific chemotherapy, the dose, and regimen of administration.⁴ Cisplatin is the chemotherapeutic agent most commonly associated with profound nausea and vomiting that follows a distinct pattern of both an acute period (generally considered the first 24 hours) and a delayed period (days 2 to 5 post chemotherapy).⁵ Severe acute emesis occurs in nearly all patients who receive cisplatin at a dose of greater than 50 mg/m² in the absence of prophylactic antiemetics;⁶ delayed emesis has been reported in 57% to 89% of patients⁷⁻⁹ with maximal intensity on days 2 and 3 after cisplatin chemotherapy.^{10,11}

Selective 5-HT₃ antagonists such as ondansetron, granisetron, tropisetron, and dolasetron administered by themselves improved the prevention of acute chemotherapy-induced emesis.¹²⁻¹⁴ However, superior prevention of acute emesis presently is achieved with the combination of a

From Merck Research Laboratories, Rahway, NJ; San Isidro Central Hospital, Buenos Aires, Argentina; Instituto de Enfermedades Neoplásicas, Lima, Peru; Instituto do Cancer, Arnaldo Vieira de Carvalho, Sao Paulo, Brazil; Ciudad Universitaria, Caracas, Venezuela; Fundacion Arturo Lopez Perez, Santiago, Chile; Instituto Nacional de Cancerologia; ISSSTE, Mexico City, Mexico.

Submitted July 31, 2000; accepted December 1, 2000.

Supported in part by funding from Merck & Co., Inc.

Address reprint requests to Barry J. Gertz, MD, PhD, Clinical Pharmacology, RY33-600, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065; e-mail barry_gertz@merck.com.

© 2001 by American Society of Clinical Oncology.

0732-183X/01/1906-1759

5-HT₃ antagonist and dexamethasone.¹⁵⁻¹⁷ Despite these advances, the 5-HT₃ antagonists are not very effective as monotherapy in preventing delayed emesis.^{18,19} The most effective therapy to prevent delayed emesis is the combination of a 5-HT₃ antagonist or metoclopramide with dexamethasone.^{20,21} However, these regimens have only recently received a consensus recommendation.²² Furthermore, even with this combination, approximately 50% of patients receiving high-dose cisplatin continue to suffer delayed vomiting and/or nausea. In addition, the combinations require multiple daily dosing, and metoclopramide can be associated with sedation and extrapyramidal side effects. Thus, simplification and improvement in the prevention of delayed emesis may be achievable.

Substance P is one of four mammalian tachykinins found in neurons (including vagal afferent fibers) innervating the brainstem nucleus tractus solitarius and the area postrema. Both regions are intimately involved in the induction of vomiting.²³ Exogenous Substance P applied to cells in the nucleus tractus solitarius results in emesis.²⁴ Substance P mediates its biologic effects through the NK₁-receptor, a G-protein receptor coupled to the inositol phosphate signal transduction pathway.²⁵

NK₁ receptor antagonists first revealed antiemetic activity in ferrets²⁶⁻²⁹ and subsequently in patients receiving cancer chemotherapy, but the optimum regimen and combination with other prophylactic antiemetics remains undefined.³⁰⁻³² L-758,298, the intravenous prodrug of the potent, selective, and orally active NK-1 antagonist MK-869 prevented acute emesis after administration of cisplatin to a degree comparable with intravenous ondansetron.³¹ However, monotherapy with either compound was not optimum for preventing acute emesis, and L-758,298 yielded unexpected benefits in reducing delayed emesis.³¹ When oral MK-869 was added to a 5HT₃ antagonist plus dexamethasone, superior control of acute emesis was achieved compared with the latter two drugs alone, and delayed emesis was again more effectively controlled.³² These findings led to the question of whether the 5HT₃ antagonist was an essential component of the regimen to achieve optimum prevention of acute and delayed emesis.

The objectives of the present study were as follows: (1) to confirm the benefit of the NK₁-receptor antagonist MK-869 in the prevention of delayed emesis secondary to cisplatin, (2) to confirm whether MK-869 can enhance the acute antiemetic efficacy achieved by the combination of a 5-HT₃ antagonist with dexamethasone, and (3) to evaluate for the first time the efficacy of MK-869 in combination with dexamethasone alone for the prevention of acute and delayed emesis and compare this efficacy to dual therapy with a 5HT₃ antagonist plus dexamethasone.

Table 1. Study Design

Treatment Group	Day -1 (evening pre-cisplatin)†	Day 1 (treatment pre-cisplatin)*	Days 2 to 5‡
I	Placebo (PO)	Gra (i.v., 10 µg/kg) Dex (20 mg PO) and placebo (PO)	Placebo (PO)
II	Placebo (PO)	Gra (i.v., 10 µg/kg), Dex (20 mg PO) and MK-869 (400 mg PO)	MK-869 (300 mg PO)
III	MK-869 (400-mg PO)	Placebo (i.v.), Dex (20 mg PO) and MK- 869 (400 mg PO)	MK-869 (300 mg PO)
IV	Placebo (PO)	Placebo (i.v.), Dex (20 mg PO) and MK- 869 (400 mg PO)	MK-869 (300 mg PO)

Abbreviations: Gra, granisetron; Dex, dexamethasone; i.v., intravenous.

*Intravenous granisetron or placebo and oral dexamethasone 30 minutes before receiving cisplatin; oral MK-869 or placebo 2 hours before receiving cisplatin; cisplatin (≥ 70 mg/m²) infused over 3 hours or less.

†Dosed at bedtime with a light snack.

‡On day 2, MK-869 or placebo was administered approximately 24 hours after initiation of the cisplatin infusion and in the morning between 0800-1000 hours on subsequent days.

PATIENTS AND METHODS

Study Design

This double-blind, multicenter, four parallel-group study was conducted in cisplatin-naïve male and female patients with cancer. The study protocol was approved by the local ethical committee in each of the participating centers, and all patients provided written informed consent. Patients were assigned to one of four treatment groups according to a computer-generated, randomized allocation schedule that incorporated stratification for both sexes and whether or not patients received additional highly emetogenic therapy (Table 1). The additional chemotherapy, included as highly emetogenic, was based on a published classification.³³

Patient Eligibility

Patients (≥ 16 years old) scheduled to receive their first course of cisplatin-based chemotherapy at a dose of greater than or equal to 70 mg/m² were enrolled. Female patients of reproductive potential demonstrated a negative assay for serum β -human chorionic gonadotropin at the prestudy visit. Primary criteria for exclusion included the following: a Karnofsky score less than 60; allergy or intolerance to metoclopramide, dexamethasone, or granisetron; use of another antiemetic agent within 72 hours of study day 1 (serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, metoclopramide, corticosteroids, or lorazepam); an episode of vomiting or retching within 24 hours before the start of the cisplatin infusion on study day 1; treatment for or history of a seizure within the past 2 years; severe concurrent illness other than neoplasia; gastrointestinal obstruction or an active peptic ulcer; radiation therapy to the abdomen or pelvis within 1 week before or after study day 1; or one of the following laboratory measurements: hemoglobin less than 8.5 g/dL, WBC less than 3,500/ μ L, platelets less than 100,000/ μ L, AST more than 2 \times ULN (upper limit of normal), ALT more than 2 \times ULN, bilirubin more than 2 \times

ULN, alkaline phosphatase more than $2 \times$ ULN, albumin less than 3 g/dL, and serum creatinine more than 2.0 mg/dL.

Treatments

The four treatment groups (I-IV) are summarized in Table 1. Rescue therapy (metoclopramide [20 to 30 mg orally four times daily or 1 to 2 mg/kg intravenously four times daily] for day 1 and dexamethasone [8 mg orally twice a day] for days 2 to 5) was permitted on an as-needed basis at any time for all patients, but was not administered prophylactically. The investigator could also prescribe metoclopramide in addition to dexamethasone as rescue therapy for days 2 to 5.

Assessments

Episodes of vomiting or retching (date, time, and number of episodes) were recorded by the patients on diary cards. An emetic episode was defined as a single vomit or retch, or any number of continuous vomits or retches; distinct episodes were separated by at least 1 minute. The primary efficacy parameter was the proportion of patients without emesis in the delayed phase (days 2 to 5). Emetic episodes were also recorded and evaluated in the acute phase (first 24 hours after initiation of cisplatin).

Nausea was assessed every 24 hours in the patient diary using a 100-mm horizontal visual analog scale that was headed: "How much nausea have you had over the last 24 hours?" Zero mm on the scale was labeled "no nausea"; 100 mm was labeled "nausea as bad as it could be."

Global satisfaction with the antiemetic treatment was assessed by the patient the morning of day 2 and the morning of day 6 post-cisplatin, using a 100-mm horizontal visual analog scale. The scale for day 2 was headed: "How satisfied are you with your antiemetic treatment over the past 24 hours?" Zero mm on the scale was labeled "not at all satisfied"; 100 mm was labeled "completely satisfied." The scale for day 6 was headed: "How satisfied are you with your antiemetic treatment over the entire study period?" Zero mm on the scale was labeled "not at all satisfied"; 100 mm was labeled "completely satisfied."

Adverse events other than episodes of vomiting and nausea were recorded by the patients on diary cards from study day -1 to 5. Adverse events including episodes of vomiting and nausea from study day 6 to their poststudy visit (study day 17 to 29) were also recorded. Patients were evaluated before chemotherapy and once on study day 6 to 8 and once again on day 17 to 29 for laboratory safety (routine hematology, serum chemistry, and urinalysis), ECGs, and physical examinations.

Statistical Analysis

The statistical analysis approach for efficacy was intent-to-treat (all patients that had data after cisplatin administration were included). The incidence of emesis in the acute and delayed periods as well as the use of rescue medication in both periods was evaluated. Fisher's exact test was used to compare the proportion of patients without emesis (and the proportion of patients without emesis or use of rescue) among the treatment groups. Data are also reported on the proportions of patients with one to two emetic episodes and three or more emetic episodes in the delayed period. Nominal *P* values and exact two-sided confidence intervals are reported for all relevant comparisons, in the delayed and also in the acute period. A separate hypothesis addressed the question of whether administration of MK-869 on day -1 (before chemotherapy) followed by MK-869 and dexamethasone on day 1, and dual therapy (MK-869 and dexamethasone) on day 1 only would be no worse than the administration of a 5HT₃ antagonist and dexamethasone

on day 1 only (groups III and IV *v* group I), as assessed by the percentage of patients reporting no emesis in the acute period. To test this hypothesis, an exact two-sided 90% confidence interval regarding the corresponding difference (group III *v* group I, and group IV *v* group I) in the proportion of patients without acute emesis is reported. The inference is based on the lower limit of the 90% confidence interval. An exploratory multifactorial analysis was conducted to investigate the relationship between the control of acute and delayed emesis. The proportion of patients that were without emesis during the delayed period but had experienced at least one emetic episode in the acute period was compared among the treatment groups. Nominal *P* values are reported.

A secondary efficacy parameter was patient self-assessment of nausea. In the analysis for days 1 to 5 and days 2 to 5, an average score was computed for each patient using the visual analog scale values over the given interval, while the analyses for the acute period and for day 2 only used the corresponding ratings recorded. Because of a nonnormal distribution of values, nonparametric analyses were performed on the ranked scores. For the intervals (days 1 to 5 and 2 to 5), the distributions of these average scores were compared among the treatment groups, using the Kruskal-Wallis χ^2 test, and median values for these distributions are reported. Additionally, pairwise comparisons were performed using the Wilcoxon test. Also, pairwise comparisons were performed for the proportions of patients that had no or minimal nausea (defined post hoc as a visual analog scale rating that averaged less than 5 mm over the entire time interval) for the intervals days 1 to 5 and days 2 to 5, using Fisher's exact test. Nominal *P* values are reported.

An exploratory parameter was patient global satisfaction with the antiemetic therapy. The groups were compared using a nonparametric analysis on the ranked scores, and medians are reported. The primary hypothesis of the study was that a comparable proportion of patients in groups I and III would be without acute emesis. The study had 80% power as designed (75 completing patients per group) to demonstrate comparability between groups I and III (predefined as within \pm 20 percentage points) for the proportion of patients without acute emesis assuming an 80% response rate in group I.

RESULTS

Patient Characteristics and Inclusion in the Analysis

The baseline characteristics of the patients assigned to the four treatment groups were similar (Table 2). A total of 354 patients received an allocation number, but three did not receive study medication (1 patient withdrew consent, one vomited within 24 hours before the first dose of drug and one patient forgot to take the day -1 medication and received no further medication). Of the 351 patients who received study medication, four were excluded from both the acute and delayed analysis because no data were collected (two took day -1 study drug but vomited before the cisplatin infusion [one each in groups II and IV]; one took day -1 study drug but discontinued before the cisplatin infusion because of a fever [group IV]; and one took day -1 study drug but discontinued before the cisplatin because he withdrew consent [group II]). One patient was included in the acute but excluded from the delayed analysis (withdrew consent on day 2, resulting in complete data only for

Table 2. Baseline Patient Characteristics

Treatment Group	Group			
	Group I	Group II	Group III	Group IV
No. of patients	90	86	89	86
Male:female, %	58:42	50:50	61:39	60:40
Age, years*	55 ± 16	53 ± 14	54 ± 14	54 ± 13
Alcohol intake, % of patients†				
0-4 drinks/wk	84	86	83	86
5-10 drinks/wk	6	4	7	5
≥11 drinks/wk	10	9	10	9
Cisplatin dose, mg/m ² *	90 ± 12	87 ± 15	89 ± 13	89 ± 12
Additional highly emetogenic chemotherapy, %‡	24	27	24	21
Type of cancer, % of patients				
Lung	39	36	45	48
Gastrointestinal	3	4	1	4
Head and neck	23	20	16	17
Genitourinary	30	33	31	30
Other	5	7	7	1

*Mean ± SD.

†If numbers do not add up to 100%, information was unavailable.

‡Use of additional highly emetogenic chemotherapy as classified by Hesketh et al.³³.

the acute analysis [group III]). The primary intent to treat efficacy analysis included 23 patients from a study center at which blinding to the granisetron/placebo infusion on day 1 could not be assured as well as nine patients who were on medications with antiemetic activity and one patient who did not receive dexamethasone on day 1. However, the statistical analyses and the study conclusions were similar when these patients were excluded. All treated patients were included in the analysis of laboratory and clinical safety parameters.

Emesis Prevention

Triple therapy with granisetron, dexamethasone, and MK-869 (group II) provided the best control of acute emesis. The proportion of patients in group II without emesis was significantly greater than that of the standard therapy group (group I) that received granisetron and dexamethasone (80% v 57%; $P < .01$) (Fig 1). The difference between groups I and II was 23 percentage points (95% exact confidence interval for this difference: 8%, 38%). Dual therapy with granisetron plus dexamethasone on day 1 (group I) yielded a numerically superior control of acute emesis, compared with the groups that received dual therapy with MK-869 plus dexamethasone (group I, 57%; group III, 46%; and group IV, 43%). In addressing the comparison between groups III and I (the primary comparability hypothesis of the trial), a 90% confidence interval

for the difference was calculated: -24% to 2%. This indicates that the two treatments were not comparable as predefined and suggests that the control of acute emesis with MK-869 plus dexamethasone could be less than that with granisetron plus dexamethasone.

Similar results for the prevention of acute emesis were achieved when considering the proportion of patients without emesis or use of rescue medication in the acute period:

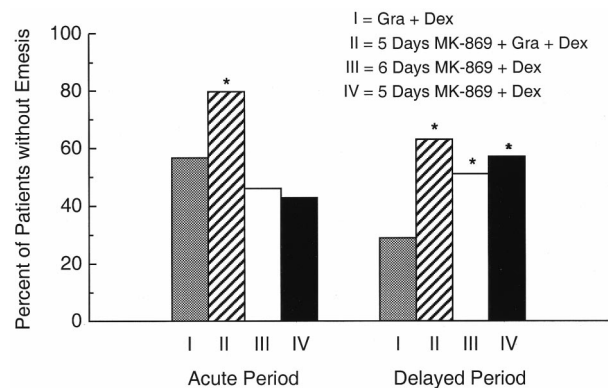


Fig 1. Percentage of patients without emesis in the acute and delayed periods irrespective of the use of rescue medication. Gra (granisetron) and Dex (dexamethasone) both administered on day 1 only. * Significantly different from group I ($P < .01$ in the acute phase, and $P < .01$ in the delayed phase).

75% of patients in group II versus 51% of patients in group I ($P < .01$). This difference between group II and group I was 24 percentage points (95% exact confidence interval for this difference; 9%, 39%). The proportions of patients without acute emesis or use of rescue medication in groups III and IV were 44% and 41%, respectively.

During the delayed period, the optimum control of emesis was achieved in those patients who received MK-869 (groups II, III, and IV). The primary comparison of interest was the incidence of delayed emesis in group II, which received MK-869, versus group I which received placebo after day 1. MK-869 treatment significantly increased the proportion of patients without delayed emesis (63% v 29%, for group II v group I, respectively; $P < .01$). The difference in the proportion of patients without delayed emesis between groups II and I was 34 percentage points (95% exact confidence interval for this difference: 19%, 49%). The prevention of delayed emesis in groups III and IV, which received MK-869 over 5 or 6 days, respectively, was also significantly superior to that observed in group I (proportion of patients without delayed emesis in groups III and IV was 51% and 57%, respectively; $P < .01$ for group III or IV v group I) (Fig 1). Significant differences in the proportion of patients without emesis or use of rescue medication in the delayed period were similarly evident (22%, 41%, 39%, and 39% in groups I through IV, respectively; $P < .05$ for group II, III, or IV v group I) (Table 3). When considering zero to two delayed emetic episodes, the incidence in groups I, II, III, and IV was 57%, 79%, 72%, and 77%, respectively ($P < .01$ for group II v group I).

The reduction in delayed emesis achieved by adding MK-869 to a regimen of a 5HT₃ antagonist plus dexamethasone was not simply the result of better control of acute emesis. This is revealed most clearly when one examines the greater frequency with which patients reported no delayed emesis in groups III and IV compared with group I, despite the fact that groups III and IV performed numerically worse than group I for acute emesis. To further substantiate this claim, the proportion of patient without emesis in the delayed period was computed using only those patients that experienced at least one emetic episode in the acute period. The percentage of patients that achieved prevention of delayed emesis, even though they had reported acute emesis, was significantly higher in group IV and numerically higher in group III versus group I (13%, 30% and 35% in groups I, III, and IV; $P < .01$ for group IV v group I).

Nausea Assessment

Median nausea visual analog scale ratings over time are displayed in Fig 2. Table 4 provides the median nausea

Table 3. Proportion of Patients With or Without Emesis in the Delayed Period (days 2 to 5)

Treatment Group	No.	Without Emesis (%)	Without Emesis or Use of Rescue (%)	1-2 Emetic Episodes (%)	≥3 Emetic Episodes (%)
I Placebo + Gra and Dex (on day 1)	90	29	22	28	43
II 5 Days MK-869 + Gra and Dex (on day 1)	84	63†	41*	16	21
III 6 days MK-869 + Dex (on day 1)	88	51†	39*	21	28
IV 5 days MK-869 + Dex (on day 1)	84	57†	39*	20	23

Abbreviations: Gra, granisetron; Dex, dexamethasone.

*Significantly different from treatment group I ($P < .05$).

†Significantly different from treatment group I ($P < .01$).

visual analog scale ratings over the intervals days 1 to 5 (acute plus delayed periods) and days 2 to 5 (delayed period only), as well as for the first 24 hours (acute period) and day 2 only (generally maximum day of nausea in delayed period). In the first 24 hours rank analysis, nausea ratings were significantly lower for group II (triple therapy on day 1) compared with group I (granisetron plus dexamethasone only on day 1) ($P < .05$). For both cumulative nausea assessments, days 1 to 5 and days 2 to 5, the distribution of

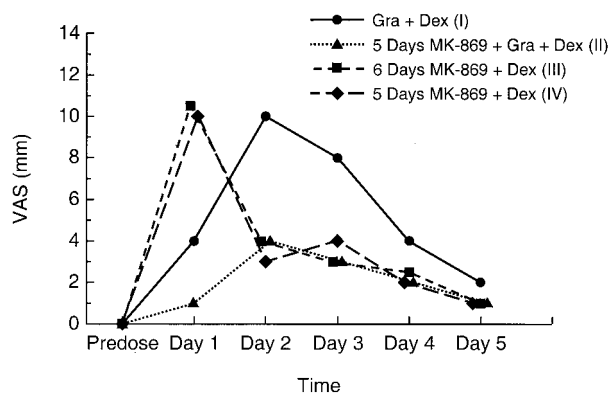


Fig 2. Median visual analog scale nausea scores over time irrespective of the use of rescue medication. Gra (granisetron) and Dex (dexamethasone) both administered on day 1 only. Groups I and II were significantly different when comparing the interval days 1 through 5, and days 2 through 5 ($P < .05$).

Table 4. Median Visual Analog Scale Nausea Scores (mm) in the Acute and Delayed Periods

Treatment Group	Acute (first 24 hours)	Acute + Delayed (days 1 to 5)	Delayed (days 2 to 5)	Delayed (day 2 only)
I Placebo + Gra and Dex (on day 1)	7.5	7	7	12
II 5 days MK-869 + Gra and Dex (on day 1)	1*	2*	2*	4
III 6 days MK-869 + Dex (on day 1)	8.5	3	3*	5
IV 5 days MK-869 + Dex (on day 1)	9.5	3	3	3*

Abbreviations: Gra, granisetron; Dex, dexamethasone.

* $P < .05$ versus group I.

nausea scores was lower in group II (triple therapy on day 1 followed by MK-869) compared with group I (granisetron plus dexamethasone only on day 1 followed by placebo) ($P < .05$ for comparison on days 1 to 5; $P = .05$ for comparison on days 2 to 5). The distribution of nausea scores was also significantly lower in group III compared with group I for the day 2 to day 5 analysis ($P < .05$). In the day 2 only rank analysis, nausea ratings in groups II, III, and IV were numerically lower than in group I, but statistical significance was achieved only for group IV versus group I ($P < .05$). The frequency with which patients had no or minimal nausea (Visual Analogue Scale average rating ≤ 5 mm) in groups I, II, III, and IV for days 1 through 5 were 36%, 50%, 41% and 44%, respectively, and for days 2 through 5, the frequencies were 38%, 52%, 45% and 49%, respectively ($P < .07$ for group II v group I, days 1 to 5 and days 2 to 5).

Global Satisfaction Assessment

The median global satisfaction ratings 24 hours after cisplatin in groups I, II, III, and IV were 94, 98, 96 and 96 mm, respectively, while the overall median global satisfaction ratings (rated on day 6) in groups I, II, III, and IV were 92, 95, 96 and 98 mm, respectively. No significant differences were observed among the groups at either time point.

Safety

All 350 patients who received study medication were included in the analysis of safety. Table 5 lists the most

common clinical adverse events (occurring in $> 10\%$ of patients in at least one treatment group) reported through study days 6 to 8 (after the last dose of study medication). These clinical adverse events included constipation, diarrhea, abdominal pain, dizziness, headache, hiccups, asthenia, and anorexia. There were no significant differences in the incidence of these adverse events among the four groups except for a higher incidence of diarrhea in the groups that did not receive granisetron on day 1 (groups III and IV). No significant differences were observed among the treatment groups with respect to laboratory indices of safety (on the basis of an analysis of the proportion of patients in each group with National Cancer Institute grade 3 or 4 toxicity for laboratory parameters³⁴). A similar pattern in the clinical and laboratory adverse experiences emerged when looking at the entire study period (day 1 through the last study visit between day 17 to 29) with comparable frequencies of adverse events among all treatment groups (data not shown).

DISCUSSION

The 5-HT₃ antagonists in combination with dexamethasone have greatly reduced, but not eliminated, acute chemotherapy-induced emesis and nausea and have been less successful in reducing delayed nausea and vomiting caused by highly emetogenic agents such as cisplatin.¹⁵⁻²¹ The present trial confirms previous findings³² that addition of the selective orally active NK₁ antagonist, MK-869, to the standard therapy of granisetron plus dexamethasone before cisplatin, reduced the incidence of acute emesis compared with dual therapy with granisetron plus dexamethasone alone. Furthermore, addition of MK-869 before and continuing after cisplatin significantly reduced emesis and nausea in the delayed period. Finally, although the combination of the 5-HT₃ antagonist plus dexamethasone seemed superior to the combination of MK-869 plus dexamethasone for the control of acute emesis, MK-869 still conferred significant benefit in reducing delayed emesis and nausea.

Acute emesis was reduced most effectively by the triple therapy regimen. During the acute period, addition of MK-869 to the regimen of granisetron plus dexamethasone increased the proportion of patients without emesis by 23 percentage points compared with the current standard of care—ie, granisetron plus dexamethasone alone (80% v 57% for group II v group I, respectively). The frequency with which patients reported no acute emesis in the standard therapy group I (57%) was comparable with that found in previous trials.³⁴⁻³⁶ Although dual therapy with MK-869 and dexamethasone (administered either just before cisplatin [group IV], or just before as well as the evening before chemotherapy [group III]) seemed to offer less protection than the standard regimen (group I), it nonetheless seemed

Table 5. Number and Percentage of Patients With Most Common Clinical and Laboratory Adverse Events

Adverse event*	Treatment Group							
	Group I		Group II		Group III		Group IV	
	No.	%	No.	%	No.	%	No.	%
Constipation	14	16	14	16	13	14	11	13
Diarrhea	15	17	14	16	36	40	31	36
Abdominal pain	19	21	13	15	12	13	11	13
Dizziness	20	22	13	15	19	21	16	18
Headache	30	33	23	27	22	24	20	23
Hiccups	14	16	18	21	19	21	22	26
Asthenia/fatigue	28	31	19	22	20	22	19	22
Anorexia	19	21	13	15	16	18	15	17
Hematologic decrease†								
Total WBC	0	0	0	0	4	5	0	0
Neutrophils	3	3	1	1	4	5	0	0
Transaminase elevations‡								
AST	0	0	2	3	1	1	0	0
ALT	4	5	5	6	1	1	0	0

Abbreviations: Gra, granisetron; Dex, dexamethasone.

*Listing of adverse events reported from postdose day 1 through follow-up day 6 to 8 regardless of relationship to study drug occurring in >10% of patients in any treatment group.

†Transient changes for WBC less than 2000 per mL and neutrophils less than 1000 per mL in patients who had normal or above normal baseline values (NCI grades 3 or 4).

‡Transient increases to more than 2.5 times the upper limit of the normal range in patients who had normal or below normal baseline values (NCI toxicity grades 2, 3, or 4).

to be an effective antiemetic combination, given that severe acute emesis occurs in virtually all patients who receive cisplatin doses greater than 50 mg/m² in the absence of prophylactic antiemetics.⁶ It also seems that the additional dose of MK-869 provided the evening before cisplatin conferred no further benefit in reducing acute emesis (compare groups III and IV). These data confirm previous findings reported with MK-869³² and suggest that an NK₁-antagonist should be used as part of a triple therapy regimen to optimally prevent acute emesis.

Delayed emesis was reduced most effectively by those regimens that included MK-869. In the delayed period, once daily oral doses of MK-869 increased the proportion of patients without emesis by 34 percentage points compared with the parallel treatment with placebo (63% v 29% for group II v group I, respectively). These results for delayed emesis were as good or better than results reported with regimens that are more complex requiring multiple drugs with repeated dosing during the day and that may not be tolerated by some patients.^{20,21} Given the less than optimum efficacy of the dual therapy groups of MK-869 and dexamethasone in preventing acute emesis, the fairly robust response in preventing delayed emesis in all groups receiving MK-869 on days 2 to 5 cannot be merely attributed to a carryover effect from better control in the acute period. The multifactorial analysis further supports the unique benefit of

MK-869 in reducing delayed emesis. These observations also suggest that the underlying mechanisms of acute and delayed emesis may be different. The absence of a study arm that included only a single (day 1) dose of MK-869 precludes any definitive conclusion regarding the need to treat for multiple days to maximally reduce delayed emesis. The observation that single doses of an NK-1 antagonist can yield benefit in the delayed period post-cisplatin³⁰⁻³² demonstrates the need for further studies designed specifically to address this question.

Nausea remains a persistent problem for many patients after chemotherapy. In the acute period, triple therapy (group II) significantly reduced nausea more than the standard therapy group (group I). In the delayed period, group II showed significant improvement over group I during the entire interval (days 2 to 5) and was marginally significantly different on day 2, the day of peak nausea. However, when the entire treatment period (days 1 to 5) is considered, triple therapy followed by once daily MK-869 (group II) manifested superior control of nausea compared with the group not receiving the NK₁-antagonist (groups II v group I; *P* < .05).]

Regimens of MK-869 were generally well tolerated with clinical and laboratory adverse events similar to the standard therapy group (group I) except for a somewhat higher incidence of diarrhea in the MK-869 groups that did not

receive granisetron (groups III and IV). Cisplatin may cause diarrhea in up to 60% of patients when administered in the absence of antiemetics.³⁴ Inclusion of prophylactic antiemetic therapy with a 5-HT₃ antagonist resulted in a lower incidence of cisplatin-related diarrhea, consistent with a constipating effect for the 5-HT₃ antagonists.³⁵ The observation of the current trial thus likely reflects the loss of this "protective" influence in the groups that did not receive granisetron. In normal volunteer studies, MK-869 administration has not resulted in diarrhea (Merck Research Laboratories, data on file).

It should be noted that subsequent to the initiation of this trial (protocol approved March 1997; first patient in the trial September 1997; last patient out of the trial March 1998), a consensus conference was held on recommended antiemetic prophylaxis for cancer chemotherapy. The results of this consensus conference were recently published²² and included the combination of either a 5HT₃ antagonist plus dexamethasone, or metoclopramide plus dexamethasone for use in the delayed period post high-dose cisplatin. The conference also recognized that control of delayed emesis is an area requiring further improvement and therapeutic alternatives.²² In light of these suggestions, only comparisons to other active agents would be appropriate for future clinical trials.

Subsequent to the completion of this study, it was determined that MK-869 reduces the clearance and thereby increases the systemic exposure to dexametha-

sone (Merck Research Laboratories, data on file). With the regimen used in the current study, one might observe as much as a 2.5-fold mean increase in dexamethasone concentration on day 1. Given that a 20-mg dose of dexamethasone has been shown to yield maximum benefit when added to a 5HT₃ antagonist,³⁷ it is unlikely that this interaction would meaningfully influence the results of the present trial, although this possibility cannot be ruled out.

In summary, the addition of oral MK-869 to granisetron plus dexamethasone before chemotherapy provided further protection against acute vomiting compared to dual therapy with just the 5-HT₃ antagonist and dexamethasone. In addition, once daily oral doses of MK-869 substantially reduced delayed emesis and nausea after high-dose cisplatin therapy. While MK-869 plus dexamethasone was not quite as effective as the 5HT₃ antagonist plus dexamethasone in reducing acute emesis, it nonetheless provided superior protection in the delayed period. Whether this reflects differences in the underlying mechanism(s) of acute and delayed emesis, as suggested by earlier studies,^{31,32} cannot be discerned from the current trial given its design. Future studies including an active comparator in the delayed phase will more directly address this question. The NK₁-antagonist MK-869 thus represents a valuable new approach and novel mechanism of action for the prevention of emesis in patients receiving highly emetogenic cancer chemotherapy including cisplatin.

REFERENCES

- Osoba D, Zee B, Warr D, et al: Quality of life studies in chemotherapy-induced emesis. *Oncology* 53(suppl 1):92-95, 1996
- Griffin AM, Butow PN, Coates AS, et al: On the receiving end: V. Patient perceptions of the side effects of cancer chemotherapy. *Ann Oncol* 7:189-195, 1997
- Laszlo J, Lucas VSJ: Emesis as a critical problem in chemotherapy. *N Engl J Med* 305:948-949, 1981
- Gralla RJ: Controlling emesis in patients receiving cancer chemotherapy. *Recent Results Cancer Res* 121:68-82, 1991
- Gralla RJ, Tyson LB, Kris MG, et al: The management of chemotherapy-induced nausea and vomiting. *Med Clin North Am* 71:289-301, 1987
- Kris MG, Cubeddu LX, Gralla RJ, et al: Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. *Cancer* 78:2193-2198, 1996
- Passalacqua R, Cocconi G, Bella M, et al: Double-blind, randomized trial for the control of delayed emesis in patients receiving cisplatin: Comparison of placebo vs. adrenocorticotrophic hormone (ACTH). *Ann Oncol* 3:481-485, 1992
- Gandara DR, Harvey WH, Monaghan GG, et al: Delayed emesis following high-dose cisplatin: A double-blind randomized comparative trial of ondansetron (GR 38032F) versus placebo. *Eur J Cancer* 1993;29A(suppl 1):S35-S38
- Kris MG, Gralla RJ, Tyson LB, et al: Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 7:108-114, 1989
- Kris MG, Gralla RJ, Clark RA, et al: Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. *J Clin Oncol* 3:1379-1384, 1985
- Navari RM, Madajewicz S, Anderson N, et al: Oral ondansetron for the control of cisplatin-induced delayed emesis: A large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. *J Clin Oncol* 13:2408-2416, 1995
- De Mulder PH, Seynaeve C, Vermorken JB, et al: Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, crossover study. *Ann Intern Med* 113:834-840, 1990
- Kris MG: Phase II trials of ondansetron with high-dose cisplatin. *Semin Oncol* 19:23-27, 1992
- Ruff P, Paska W, Goedhals L, et al: Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: A multicenter double-blind, randomized, parallel-group study. *Oncology* 51:113-118, 1994
- Roila F, Tonato M, Cognetti F, et al: Prevention of cisplatin-induced emesis: A double-blind multicenter randomized crossover

study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 9:675-678, 1991

16. Smith DB, Newlands ES, Rustin GJS, et al: Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 338:487-490, 1991

17. Hesketh PJ, Harvey WH, Harker WG, et al: A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. *J Clin Oncol* 12:596-600, 1994

18. Roila F, Bracardia S, Tonato M, et al: Ondansetron in the prophylaxis of acute and delayed cisplatin-induced emesis. *Clin Oncol* 2:268-272, 1990

19. Hesketh P: Management of cisplatin-induced delayed emesis. *Oncology* 53(suppl 1):78-85, 1996

20. Kris MG, Gralla RJ, Tyson LB, et al: Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 7:108-114, 1989

21. Gralla RJ, Rittenberg C, Peralta M, et al: Cisplatin and emesis: Aspects of treatment and a new trial for delayed emesis using oral dexamethasone plus ondansetron beginning at 16 hours after cisplatin. *Oncology* 53(suppl 1):86-91, 1996

22. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of Perugia Consensus Conference. *Ann Oncol* 9:811-819, 1998

23. Borison HL, McCarthy LE: Neuropharmacology of chemotherapy induced emesis. *Drugs* 25:8-17, 1983

24. Gardner CJ, Bountra C, Bunce KT, et al: Anti-emetic activity of neurokinin NK1 receptor antagonists is mediated centrally in the ferret. *Br J Pharmacol* 112:516P, 1994

25. Otsuka M, Yoshioka K: Neurotransmitter functions of mammalian tachykinins. *Physiol Rev* 73:229-308, 1993

26. Tattersall FD, Rycroft W, Francis B, et al: Tachykinin NK₁ receptor antagonists act centrally to inhibit emesis induced by the

chemotherapeutic agent cisplatin in ferrets. *Neuropharmacology* 35: 1121-1129, 1996

27. Gardner CJ, Armour DR, Beattie DT, et al: GR205171: A novel antagonist with high affinity for the tachykinin NK₁ receptor, and potent broad-spectrum anti-emetic activity. *Regul Pept* 65:45-53, 1996

28. Singh L, Field MJ, Hughes J, et al: The tachykinin NK₁ receptor antagonist PD 154075 blocks cisplatin-induced delayed emesis in the ferret. *Eur J Pharmacol* 321:209-216, 1997

29. Tattersall FD, Rycroft W, Cumberbatch M, et al: The novel NK₁ receptor antagonist MK-0869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. *Neuropharmacology* 39:4, 2000.:652-663

30. Kris MG, Radford JE, Pizzo BA, et al: Use of an NK₁ receptor antagonist to prevent delayed emesis after cisplatin. *J Natl Cancer Inst* 89:817-818, 1997

31. Van Belle S, Cocquyt V, De Smet M, et al: Comparison of a neurokinin-1 antagonist L-758,298 to ondansetron in the prevention of cisplatin-induced emesis. *Prog Proc Am Soc Clin Oncol* 17:198a, 1998 (abstr)

32. Navari R, Reinhardt RR, Gralla RJ, et al: Reduction of cisplatin-induced emesis by a selective neurokinin-1 receptor antagonist. *N Engl J Med* 340:190-195, 1999

33. Hesketh PJ, Kris MG, Grunberg SM, et al: Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 15:103-109, 1997

34. Gralla RJ, Itri LM, Pisko SE, et al: Antiemetic efficacy of high-dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 305:905-909, 1981

35. Physicians Desk Reference (ed 52). Montvale, NJ, Medical Economics Co, 1998, pp 2836-2838

36. National Cancer Institute: Common Toxicity Criteria, Version 2.0. Bethesda, MD, National Cancer Institute, 1998

37. Italian Group for Antiemetic Research: Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. *J Clin Oncol* 16: 2937-2942, 1998