

REDUCTION OF CISPLATIN-INDUCED EMESIS BY A SELECTIVE NEUROKININ-1-RECEPTOR ANTAGONIST

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ABSTRACT

Background The localization of substance P in brain-stem regions associated with vomiting, and the results of studies in ferrets, led us to postulate that a neurokinin-1-receptor antagonist would be an antiemetic in patients receiving anticancer chemotherapy.

Methods In a multicenter, double-blind, placebo-controlled trial involving 159 patients who had not previously received cisplatin, we evaluated the prevention of acute emesis (occurring within 24 hours) and delayed emesis (occurring on days 2 to 5) after a single dose of cisplatin therapy (70 mg or more per square meter of body-surface area). Before receiving cisplatin, all the patients received granisetron (10 μ g per kilogram of body weight intravenously) and dexamethasone (20 mg orally). The patients were randomly assigned to one of three treatments in addition to granisetron and dexamethasone: 400 mg of an oral trisubstituted morpholine acetal (also known as L-754,030) before cisplatin and 300 mg on days 2 to 5 (group 1), 400 mg of L-754,030 before cisplatin and placebo on days 2 to 5 (group 2), or placebo before cisplatin and placebo on days 2 to 5 (group 3). Additional medication was available at any time to treat occurrences of vomiting or nausea.

Results In the acute-emesis phase, 93 percent of the patients in groups 1 and 2 combined and 67 percent of those in group 3 had no vomiting ($P < 0.001$). In the delayed-emesis phase, 82 percent of the patients in group 1, 78 percent of those in group 2, and 33 percent of those in group 3 had no vomiting ($P < 0.001$ for the comparison between group 1 or 2 and group 3). The median nausea score in the delayed-emesis phase was significantly lower in group 1 than in group 3 ($P = 0.003$). No serious adverse events were attributed to L-754,030.

Conclusions The neurokinin-1-receptor antagonist L-754,030 prevents delayed emesis after treatment with cisplatin. Moreover, combining L-754,030 with granisetron plus dexamethasone improves the prevention of acute emesis. (N Engl J Med 1999;340:190-5.)

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PATIENTS consistently report that vomiting and nausea are among the most unpleasant and distressing aspects of chemotherapy.¹ Vomiting due to anticancer drugs reduces the quality of life² and may cause patients to delay or refuse potentially curative therapy.³

The severity and pattern of chemotherapy-induced emesis depend on the specific agents used, the dose,

and the regimen.⁴ Cisplatin is most commonly associated with profound nausea and vomiting, which follow a distinct pattern of an acute phase (within 24 hours after chemotherapy) and a delayed phase (on days 2 to 5).⁵ Severe acute emesis occurs in virtually all patients who receive doses of cisplatin of ≥ 50 mg per square meter of body-surface area without prophylactic antiemetics⁶; delayed emesis occurs in 57 to 89 percent, with maximal intensity on days 2 and 3 after chemotherapy.⁷⁻¹¹

Efforts to prevent chemotherapy-induced emesis have been directed at blocking neurotransmitter receptors in the brain-stem vomiting center. The chemoreceptor trigger zone in the area postrema transmits impulses to the vomiting center after the administration of chemotherapeutic agents.¹² Receptors for neurotransmitters such as dopamine, endorphin, serotonin, and substance P are found in these areas. Initial efforts focused on blocking dopamine with phenothiazines, butyrophenones, and metoclopramide (which was later found to bind the serotonin receptor).¹³ Each compound is partially effective when given as a single agent. Combinations of antiemetics, such as metoclopramide plus dexamethasone, were found to improve the prevention of chemotherapy-induced emesis significantly.¹⁴ The next major breakthrough occurred with the introduction of selective serotonin antagonists, such as ondansetron and granisetron, which have peripheral and central sites of action.

Although serotonin antagonists by themselves improve the prevention of acute chemotherapy-induced emesis,¹⁵⁻¹⁷ better control is achieved with the combination of a serotonin antagonist and dexamethasone, which completely prevents vomiting in 48 to 91 percent of patients.¹⁸⁻²⁰ However, the serotonin antagonists are not as effective against delayed emesis.^{21,22} The most effective current approach to the prevention of delayed emesis is the combination of a serotonin antagonist or metoclopramide with dexameth-

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asone, which completely prevents delayed emesis in 52 to 69 percent of patients.^{9,23} These regimens require multiple daily doses, and metoclopramide can cause sedation and extrapyramidal side effects. Thus, there is considerable opportunity for improvement in the prevention of delayed emesis.

Substance P is one of four mammalian tachykinins found in neurons, including vagal afferent fibers innervating the brain-stem nucleus tractus solitarius and area postrema. Exogenous substance P applied to cells in the nucleus tractus solitarius causes vomiting.²⁴ The biologic actions of substance P are mediated through the neurokinin-1 receptor, a G-protein receptor coupled to the inositol phosphate signal-transduction pathway.²⁵

L-754,030, a trisubstituted morpholine acetal, is a potent and selective nonpeptide neurokinin-1-receptor antagonist. Neurokinin-1-receptor antagonists inhibit emesis induced by cisplatin in ferrets, and central nervous system penetration is essential for the antiemetic activity of the drug.²⁶⁻²⁸ In ferrets, L-754,030 resulted in a dose-dependent inhibition of both acute and delayed cisplatin-induced vomiting.²⁹ Moreover, additive efficacy was achieved by combining L-754,030 with either dexamethasone or ondansetron (Tattersall FD: personal communication). Preliminary observations suggested that similar benefits might be obtained with a neurokinin-1-receptor antagonist in patients.³⁰

We undertook this study to evaluate a neurokinin-1-receptor antagonist, L-754,030, for the prevention of delayed emesis due to cisplatin; to determine whether L-754,030 enhances the acute antiemetic effect of the combination of a serotonin antagonist and dexamethasone; and to assess the safety of L-754,030.

METHODS

Study Design

The subjects of this double-blind, multicenter, placebo-controlled study were men and women with cancer who had not previously been treated with cisplatin. The patients were assigned to one of three treatment groups according to a computer-generated randomization schedule that incorporated stratification according to sex and according to whether or not the patient was receiving additional highly emetogenic therapy, as previously defined.³¹ All the patients provided written informed consent.

In all three groups, the patients received an oral dose of dexamethasone (20 mg) and an intravenous dose of granisetron (10 μ g per kilogram of body weight) 30 minutes before receiving a single dose of cisplatin (day 1). On day 1, the patients also received 400 mg of oral L-754,030 (groups 1 and 2) or placebo (group 3). The patients in group 1 also received 300 mg of L-754,030 once daily on days 2 through 5, whereas the patients in groups 2 and 3 received placebo on days 2 through 5. Rescue therapy for day 1 (20 to 30 mg of metoclopramide orally four times daily or 1 to 2 mg per kilogram intravenously four times daily) and days 2 to 5 (8 mg of dexamethasone orally twice daily with or without metoclopramide) was permitted at any time but was not given prophylactically. L-754,030 or placebo was given orally 2 hours before cisplatin infusion on day 1, approximately 24 hours after initiation of the cisplatin infusion on day 2, and on subsequent days between 8 and 10 a.m.

Eligibility

Patients were enrolled who were at least 18 years of age and who were scheduled to receive a first course of cisplatin at a dose of at least 70 mg per square meter. Women of child-bearing age had to have a negative test for the β subunit of human chorionic gonadotropin in serum. The primary exclusion criteria included a Karnofsky score of less than 60; allergy to or intolerance of metoclopramide, dexamethasone, or granisetron; therapy with another antiemetic drug (serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, metoclopramide, or glucocorticoids) within 72 hours before day 1; an episode of vomiting or retching within 24 hours before the start of the cisplatin infusion; treatment for or history of a seizure within the previous two years; severe concurrent illness other than cancer; gastrointestinal obstruction or active peptic ulcer; radiation therapy to the abdomen or pelvis within one week before or after day 1; or any of the following laboratory measurements: hemoglobin level below 8.5 g per deciliter, white-cell count below 3500 per cubic millimeter, platelet count below 100,000 per cubic millimeter, serum aspartate aminotransferase level more than twice the upper limit of normal, serum alanine aminotransferase level more than twice the upper limit of normal, serum bilirubin level more than twice the upper limit of normal, serum alkaline phosphatase level more than twice the upper limit of normal, serum albumin level below 3 g per deciliter, and serum creatinine level of more than 2 mg per deciliter (180 μ mol per liter). Five patients who were scheduled to receive palitaxel in addition to cisplatin were permitted to receive additional glucocorticoids before day 1.

Assessments

Episodes of vomiting or retching were recorded by the patients on diary cards. An emetic episode was defined as a single instance of vomiting or retching, or any number of continuous instances of vomiting or retching; distinct episodes were separated by at least one minute. The primary measure of efficacy was the proportion of patients without emesis in the delayed-emesis phase.

Nausea was assessed on a 100-mm horizontal visual-analogue scale in the patient diary with the heading "How much nausea have you had over the past 24 hours?" The left-hand end of the scale (0 mm) was labeled "no nausea," and the right-hand end (100 mm) was labeled "nausea as bad as it could be." Every 24 hours the patient indicated the degree of nausea during the previous 24 hours by placing a vertical mark on the scale line.

Global satisfaction with the antiemetic treatment was assessed on a 100-mm visual-analogue scale on the mornings of days 2 and 6 after cisplatin treatment. The scale for day 2 was headed "How satisfied are you with your anti-emetic treatment over the past 24 hours?" The scale for day 6 was headed "How satisfied are you with your anti-emetic treatment over the entire study period?" On both scales, 0 mm was labeled "not at all satisfied," and 100 mm was labeled "completely satisfied."

Adverse events were recorded up to the post-study visit, which occurred between day 17 and day 29. The patients also underwent laboratory safety studies (hematologic, serum chemical, and urine analyses), electrocardiography, and physical examinations between days 6 and 8 and between days 17 and 29.

Statistical Analysis

The statistical analysis of efficacy was performed on an intention-to-treat basis (all patients with data on emesis after the administration of L-754,030 were included). The incidence of vomiting in the acute-emesis and delayed-emesis phases and the use of rescue medication in both phases were evaluated. Fisher's exact test was used for pairwise comparison of the incidence of emesis (and no emesis or use of rescue therapy) between treatment groups. The proportions of patients with one or two and with three or more emetic episodes in the delayed-emesis phase were also summarized. A Bonferroni adjustment for multiplicity was used in testing for significance only in the analysis of emesis, since

TABLE 1. CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	DAILY L-754,030 (GROUP 1)	SINGLE-DOSE L-754,030 (GROUP 2)	PLACEBO (GROUP 3)
No. of patients	54	54	51
Male sex (%)	65	65	59
Age (yr)	64±10	61±11	60±13
No. of alcoholic drinks/wk (%)†			
0-4	80	87	80
5-10	7	7	8
≥11	9	4	10
Cisplatin dose (mg/m ²)	77±11	80±12	81±12
Additional emetogenic chemotherapy (%)	4	4	4
Type of cancer (%)			
Lung	68	69	68
Gastrointestinal	13	7	8
Head and neck	11	11	8
Genitourinary	4	11	8
Other	4	2	8

*Plus-minus values are means ±SD.

†Percentages do not total 100 because some data were missing.

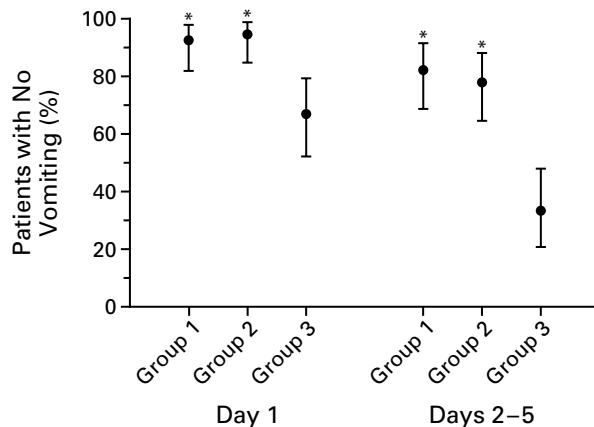


Figure 1. Percentage of Patients with No Vomiting during the Acute-Emesis (Day 1) and Delayed-Emesis (Days 2 to 5) Phases. Bars indicate 95 percent confidence intervals. All groups received granisetron and dexamethasone before receiving cisplatin. In addition, group 1 received L-754,030 before cisplatin and on days 2 to 5; group 2 received L-754,030 before cisplatin and placebo on days 2 to 5; and group 3 received placebo before cisplatin and on days 2 to 5. Asterisks indicate $P < 0.001$ for the comparisons with group 3.

emesis was the primary end point. Nominal 95 percent confidence intervals are reported. A sample size of 43 patients per group provided the study with 80 percent power to detect a 30 percentage point increase or a 25 percentage point decrease as compared with placebo in the proportion of patients without vomiting in the delayed-emesis phase (two-sided test, $\alpha = 0.05$).

A secondary measure of efficacy was the patient's self-assessment of nausea. In the analysis for days 1 to 5 and 2 to 5, an average score was calculated for each patient from the values on the visual-analogue scale over the given interval; the analysis for day 2 used the rating recorded on day 2. Because the distribution of

values was not normal, nonparametric analyses were performed on the ranked scores. For days 1 to 5 and days 2 to 5, the distributions of these average scores were compared among the treatment groups with use of the Kruskal-Wallis chi-square test, and median values for these distributions are reported. Pairwise comparisons were also made with use of the Wilcoxon test. In addition, Fisher's exact test was used to make pairwise comparisons of the proportions of patients who had no nausea or minimal nausea (defined post hoc as a rating on the visual-analogue scale that averaged less than 5 mm over the entire period) on days 1 to 5, days 2 to 5, and day 2 only.

An exploratory measure was the patient's global degree of satisfaction with the antiemetic therapy. The groups were compared with use of a general linear model and a nonparametric analysis of the ranked scores. The results of the two analyses were similar, and the medians are reported.

RESULTS

Of the 159 patients who enrolled in this study, 1 patient in group 1 was excluded from both phases of the trial, because the patient vomited before the cisplatin infusion and no data on emesis were collected. Three others in group 1 were excluded from the analysis of the delayed-emesis phase; all three withdrew from the study and provided no data on emesis for the delayed-emesis phase, one because of inability to swallow the pills and two because of lack of efficacy in the acute phase. Two patients in group 3 received glucocorticoids during the study for reasons other than rescue medication but were included in the efficacy analysis. The base-line characteristics of the patients assigned to the three treatment groups were similar (Table 1).

Prevention of Vomiting

During the acute-emesis period, the treatment that best prevented vomiting was triple therapy with granisetron, dexamethasone, and L-754,030 (groups 1 and 2). The proportion of patients who did not vomit was significantly higher in group 1 (93 percent), group 2 (94 percent), and in groups 1 and 2 combined (93 percent) than in group 3, which received the standard therapy of granisetron and dexamethasone (67 percent, $P < 0.001$ for the comparison between groups 1 and 2 combined and group 3) (Fig. 1). The difference in the proportions of patients with no emesis between groups 1 and 2 combined and group 3 was 26 percentage points (95 percent confidence interval, 12 to 43).

The proportions of patients who had no emesis and who did not require rescue therapy in group 1 (77 percent), group 2 (83 percent), and groups 1 and 2 combined (80 percent) were higher than that in group 3 (57 percent, $P = 0.004$ for the comparison between groups 1 and 2 combined and group 3). The difference between groups 1 and 2 combined and group 3 in the proportion of patients who had no emesis and who did not require rescue therapy was 23 percentage points (95 percent confidence interval, 7 to 40).

During the delayed-emesis period, the prevention of emesis was best achieved in the patients who re-

ceived L-754,030 (groups 1 and 2). The prevention of delayed emesis in groups 1 and 2 was significantly superior to that in group 3, in which placebo was given during both the acute- and delayed-emesis phases (the proportions of patients without delayed emesis in groups 1, 2, and 3 were 82 percent, 78 percent, and 33 percent, respectively; $P < 0.001$ for the comparison between group 1 or 2 and group 3) (Fig. 1 and Table 2). The difference between groups 1 and 3 in the proportion of patients who did not vomit was 49 percentage points (95 percent confidence interval, 30 to 67); between groups 2 and 3, the difference was 45 percentage points (95 percent confidence interval, 26 to 62).

There were also significant differences between the groups receiving L-754,030 and the placebo group in the proportion of patients who had no emesis and did not require rescue therapy in the delayed-emesis phase (52 percent, 43 percent, and 16 percent in groups 1, 2, and 3, respectively; $P < 0.001$ for the comparison between groups 1 and 3, and $P = 0.003$ for the comparison between groups 2 and 3) (Table 2). These percentages corresponded to differences of 36 percentage points (95 percent confidence interval, 16 to 55) between groups 1 and 3 and 27 percentage points (95 percent confidence interval, 8 to 46) between groups 2 and 3. There was no significant difference between groups 1 and 2 in the proportion of patients with delayed emesis. The proportions of patients with no more than two episodes of delayed emesis were 98 percent in group 1, 93 percent in group 2, and 59 percent in group 3 ($P < 0.001$ for the comparison between group 1 or 2 and group 3).

Assessment of Nausea

Figure 2 shows the median scores on the visual-analogue scale for nausea over time, and Table 3 gives these scores for days 1 to 5, days 2 to 5, and day 2. Over days 1 to 5 and days 2 to 5, the distribution of nausea scores was significantly lower in group 1 than in group 3 ($P = 0.003$ for both comparisons). In the analysis for day 2, the nausea scores in groups 1 and 2 were significantly lower than those in group 3 ($P = 0.002$ for group 1 vs. group 3, and $P = 0.005$ for group 2 vs. group 3). The proportions of patients with no nausea or minimal nausea in groups 1, 2, and 3 on days 1 to 5 were 49 percent, 48 percent, and 25 percent, respectively ($P = 0.02$ for group 1 vs. group 3, and $P = 0.03$ for group 2 vs. group 3); on days 2 to 5, the proportions were 51 percent, 48 percent, and 24 percent, respectively ($P = 0.007$ for group 1 vs. group 3, and $P = 0.01$ for group 2 vs. group 3); and on day 2 the proportions were 65 percent, 61 percent, and 41 percent, respectively ($P = 0.03$ for group 1 vs. group 3).

Assessment of Global Satisfaction

There was no difference among the treatment groups in the global-satisfaction rating on day 2 (the

TABLE 2. FREQUENCY OF EPISODES OF VOMITING DURING THE DELAYED-EMESIS PHASE (DAYS 2 TO 5).

TREATMENT GROUP*	NO. OF PATIENTS	NO. OF EPISODES			NO EMESIS AND NO RESCUE THERAPY
		0	1-2	≥3	
		% of patients			
Daily L-754,030 (group 1)	50	82†	16	2	52‡
Single-dose L-754,030 (group 2)	54	78†	15	7	43‡
Placebo (group 3)	51	33	26	41	16

*All the patients received granisetron and dexamethasone on day 1.
 † $P < 0.001$ for the comparison with group 3.
 ‡ $P < 0.001$ for the comparison between groups 1 and 3, and $P = 0.003$ for the comparison between groups 2 and 3.

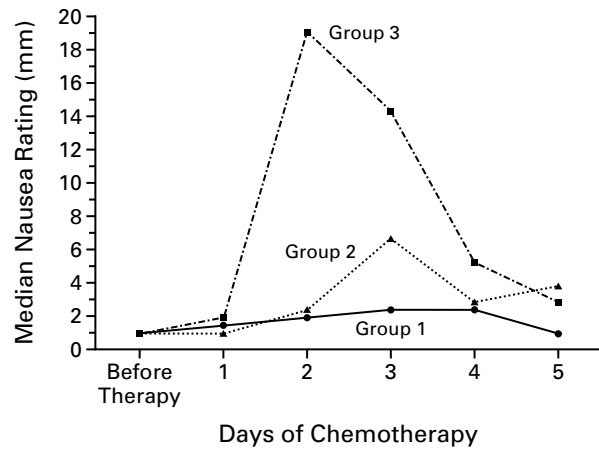


Figure 2. Median Scores on the Visual-Analogue Scale for Nausea during the Acute-Emesis (Day 1) and Delayed-Emesis (Days 2 to 5) Phases.

All groups received granisetron and dexamethasone before receiving cisplatin. In addition, group 1 received L-754,030 before cisplatin and on days 2 to 5; group 2 received L-754,030 before cisplatin and placebo on days 2 to 5; and group 3 received placebo before cisplatin and on days 2 to 5. The visual-analogue rating scale for nausea runs from 0 mm ("no nausea") to 100 mm ("nausea as bad as it could be"). The values for group 1 were significantly different from those for group 3 on days 1 to 5 and on days 2 to 5 ($P = 0.003$ for both comparisons). The values for groups 1 and 2 were significantly different from those for group 3 on day 2 ($P = 0.002$ for group 1 vs. group 3, and $P = 0.005$ for group 2 vs. group 3).

medians for groups 1 and 2 combined and for group 3 were both 100 mm). The median ratings on day 6 for global satisfaction in groups 1, 2, and 3 were 100, 98, and 82 mm, respectively. Groups 1 and 2 had significantly better ratings than group 3 ($P = 0.001$ for group 1 vs. group 3, and $P = 0.03$ for group 2 vs. group 3).

TABLE 3. MEDIAN SCORES ON THE VISUAL-ANALOGUE SCALE FOR NAUSEA DURING THE ACUTE-EMESIS AND DELAYED-EMESIS PHASES.*

TREATMENT GROUP†	ACUTE AND DELAYED			
	ACUTE (DAY 1)	DELAYED (DAYS 1-5)	DELAYED (DAYS 2-5)	DELAYED (DAY 2)
Daily L-754,030 (group 1)	0	1‡	1‡	1§
Single-dose L-754,030 (group 2)	0	2	3	2§
Placebo (group 3)	1	5	10	19

*The scale runs from 0 mm ("no nausea") to 100 mm ("nausea as bad as it could be").

†All the patients received granisetron and dexamethasone on day 1.

‡P=0.003 for the comparison with group 3.

§P=0.002 for the comparison between groups 1 and 3, and P=0.005 for the comparison between groups 2 and 3.

TABLE 4. MOST COMMON CLINICAL AND LABORATORY ADVERSE EVENTS.*

EVENT	DAILY L-754,030 (GROUP 1)	SINGLE-DOSE L-754,030 (GROUP 2)	PLACEBO (GROUP 3)
	number of patients (percent)		
Clinical events			
Constipation	10 (19)	7 (13)	9 (18)
Diarrhea	9 (17)	4 (7)	5 (10)
Dehydration	3 (6)	3 (6)	7 (14)
Headache	12 (22)	9 (17)	10 (20)
Hiccups	8 (15)	9 (17)	7 (14)
Asthenia	14 (26)	14 (26)	13 (25)
Hematologic changes†			
Decrease in total white-cell count	1 (2)	1 (2)	1 (2)
Decrease in neutrophils	0	1 (2)	1 (2)
Serum aminotransferase elevations‡			
Aspartate aminotransferase	0	0	4 (8)
Alanine aminotransferase	5 (9)	0	7 (14)

*All adverse events occurring on days 1 to 7 are listed, regardless of their relation to the study drugs. There were 54 patients in group 1, 54 in group 2, and 51 in group 3. All the patients received granisetron and dexamethasone on day 1.

†Listed are transient decreases in the white-cell count to less than 2000 per cubic millimeter and in neutrophils to less than 1000 per cubic millimeter in patients who had normal or above-normal base-line values (National Cancer Institute toxicity grade III or IV).³²

‡Listed are transient increases to greater than 2.5 times the upper limit of the normal range in patients who had normal or below-normal base-line values (National Cancer Institute toxicity grade II, III, or IV).³²

Safety

All 159 patients who received study medication were included in the analysis of safety. Table 4 lists the most common adverse events through day 7. There were no significant differences in the incidence of these events among the three groups, nor were significant differences observed with respect to laboratory indexes of safety. The same pattern in clinical and laboratory adverse events emerged when the en-

tire study period (day 1 through the last study visit between days 17 and 29) was considered, and there were no significant differences among the treatment groups.

DISCUSSION

The use of serotonin antagonists in combination with dexamethasone has greatly reduced the frequency of acute chemotherapy-induced emesis but has had less effect on delayed nausea and vomiting caused by highly emetogenic agents such as cisplatin.¹⁸⁻²³ The results of our trial demonstrate that the standard therapy (granisetron plus dexamethasone) with the addition of the selective neurokinin-1 antagonist L-754,030 is superior to the standard therapy alone in preventing acute emesis, and that L-754,030 significantly reduces the frequency of vomiting and nausea in the delayed-emesis phase.

During the acute-emesis phase, the addition of L-754,030 to granisetron plus dexamethasone increased the proportion of patients who did not vomit by 26 percentage points. In addition, significantly fewer patients used rescue medication in the triple-therapy group. In the standard-therapy group, 67 percent of the patients did not vomit, a result similar to those of previous trials. In this group, 57 percent of the patients did not vomit and did not require rescue therapy, a result that may reflect the high expectations patients now have for control of nausea and vomiting, resulting in a lower threshold for rescue therapy.³³⁻³⁵

The proportion of patients with no delayed emesis in the groups given a single dose of L-754,030 on day 1 (group 2) or daily doses of L-754,030 (group 1) was approximately 50 percentage points greater than that in the group given placebo (group 3) and was up to 30 percentage points greater than the proportions reported with the most successful complex dual-therapy regimens (52 to 69 percent of patients given serotonin antagonists or metoclopramide with dexamethasone have no emesis).^{9,23} In addition, significantly fewer patients used rescue medication when receiving multiple or single doses of L-754,030.

In the acute-emesis phase, triple therapy did not significantly reduce the frequency of nausea as compared with standard therapy. However, the group receiving daily L-754,030 had significantly less nausea in the delayed-emesis phase and over the entire study period than the placebo group. In addition, the global satisfaction of patients with their antiemetic therapy was significantly greater with L-754,030. Use of L-754,030 should improve patients' quality of life, because nausea now outranks vomiting as the most unpleasant aspect of chemotherapy.¹

During the delayed-emesis phase, the groups receiving single-dose therapy (group 2) and daily therapy (group 1) with L-754,030 did not differ significantly from each other in the proportion of patients who had no emesis. However, as compared with group 2, group 1 consistently had more patients who

had no emesis and did not require rescue therapy, lower nausea scores, and higher global-satisfaction scores. Only a larger trial can determine whether continuation of L-754,030 treatment beyond day 1 yields an improvement that is both clinically and statistically significant. An argument could be made for testing the continuation of L-754,030 therapy at least through day 3, encompassing the period during which the incidence and severity of delayed nausea and vomiting are greatest.

L-754,030 (in either single or multiple doses) was generally well tolerated, with an incidence of clinical and laboratory adverse events that was similar to that with placebo.

In summary, the addition of L-754,030 to granisetron and dexamethasone treatment before chemotherapy provided better protection against vomiting in the acute-emesis phase than the combination of dexamethasone and a serotonin antagonist alone. Moreover, single and multiple doses of L-754,030 prevented delayed emesis after high-dose cisplatin therapy. A neurokinin-1-receptor antagonist such as L-754,030 represents a new type of agent acting through a novel mechanism to prevent vomiting in patients receiving highly emetogenic chemotherapy for cancer.

Presented in part at the 34th Annual Meeting of the American Society of Clinical Oncology, Los Angeles, May 16-19, 1998.

APPENDIX

The other members of the L-754,030 Antiemetic Trials Group were F.A. Bailey and J. Hankins, SORRA Research Center, Birmingham, Ala.; F.P. Arena and H. Gerstein, Great Neck, N.Y.; S. Luedke, St. Louis Center for Clinical Research, St. Louis; S.J. Yee, Arcadia, Calif.; M. Modiano, Arizona Clinical Research, Tucson; D.F. Roychowdhury, University of Cincinnati, Cincinnati; R.C. Shepard, Medical West Oncology, Chicopee, Mass.; D.P. Gray, Columbus Regional Hospital Cancer Care, Columbus, Ind.; J.A. Reeves, Leecoast Research Center, Fort Myers, Fla.; I. Royston, Sidney Kimmel Cancer Center, San Diego, Calif.; J. Scott, Georgia Cancer Specialists, Decatur; C.J. Badolato, Associated Medical Research, Melbourne, Fla.; and W.R. Edwards, Rockford Clinic, Rockford, Ill.

REFERENCES

1. 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;7:189-95.
2. Osoba D, Zee B, Warr D, Kaizer L, Latreille J, Pater J. Quality of life studies in chemotherapy-induced emesis. *Oncology* 1996;53:Suppl 1:92-5.
3. Laszlo J, Lucas VS Jr. Emesis as a critical problem in chemotherapy. *N Engl J Med* 1981;305:948-9.
4. Gralla RJ. Controlling emesis in patients receiving cancer chemotherapy. *Recent Results Cancer Res* 1991;121:68-85.
5. Gralla RJ, Tyson LB, Kris MG, Clark RA. The management of chemotherapy-induced nausea and vomiting. *Med Clin North Am* 1987;71:289-301.
6. 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* 1996;78:2193-8.
7. 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* 1992;3:481-5.
8. Gandara DR, Harvey WH, Monaghan GG, Perez EA, Hesketh PJ. 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.
9. Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989;7:108-14.

10. 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* 1985;3:1379-84.
11. 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* 1995;13:2408-16.
12. Borison HL, McCarthy LE. Neuropharmacology of chemotherapy-induced emesis. *Drugs* 1983;25:Suppl 1:8-17.
13. Ireland SJ, Straughan DW, Tyers MB. Influence of 5-hydroxytryptamine uptake on the apparent 5-hydroxytryptamine antagonist potency of metoclopramide in the rat isolated superior cervical ganglion. *Br J Pharmacol* 1987;90:151-60.
14. Kris MG, Gralla RJ, Tyson LB, et al. Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone, and diphenhydramine: results of consecutive trials in 255 patients. *Cancer* 1985;55:527-34.
15. 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* 1990;113:834-40.
16. Kris MG. Phase II trials of ondansetron with high-dose cisplatin. *Semin Oncol* 1992;19:Suppl 4:23-7.
17. Ruff P, Paska W, Goedhals L, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicentre double-blind, randomised, parallel-group study. *Oncology* 1994;51:113-8. [Erratum, *Oncology* 1994;51:243.]
18. 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* 1991;9:675-8.
19. Smith DB, Newlands ES, Rustin GJS, et al. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991;338:487-90.
20. 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* 1994;12:596-600.
21. Roila F, Bracarda S, Tonato M, et al. Ondansetron (GR38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. *Clin Oncol (R Coll Radiol)* 1990;2:268-72.
22. Hesketh P. Management of cisplatin-induced delayed emesis. *Oncology* 1996;53:Suppl 1:73-7.
23. Gralla RJ, Rittenberg C, Peralta M, Lettow L, Cronin M. 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* 1996;53:Suppl 1:86-91.
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* 1994;112:Suppl:516P. abstract.
25. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. *Physiol Rev* 1993;73:229-308.
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* 1996;35:1121-9.
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* 1996;65:45-53.
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* 1997;321:209-16.
29. Tattersall FD, Rycroft W, Hale JJ, et al. The NK₁ receptor antagonist L-754,030 and its N-phosphoryl prodrug L-758,298 inhibit acute and delayed cisplatin-induced emesis in the ferret. *Proc Am Soc Clin Oncol* 1998;17:253a. abstract.
30. Kris MG, Radford JE, Pizzo BA, Inabinet R, Hesketh A, Hesketh PJ. Use of an NK₁ receptor antagonist to prevent delayed emesis after cisplatin. *J Natl Cancer Inst* 1997;89:817-8.
31. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;15:103-9.
32. Common toxicity criteria, version 2.0. Bethesda, Md.: National Cancer Institute, March 1998.
33. The Italian Group for Antiemetic Research. Ondansetron + dexamethasone vs metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. *Lancet* 1992;340:96-9.
34. Kris MG, Baltzer L, Pisters KMW, Tyson LB. Enhancing the effectiveness of the specific serotonin antagonists: combined antiemetic therapy with dexamethasone. *Cancer* 1993;72:Suppl:3436-42.
35. Perez EA. Comparative efficacy of oral and intravenous granisetron for the prevention of acute chemotherapy-induced emesis. *Clin Ther* 1996;18:578-90.