

DEXAMETHASONE ALONE OR IN COMBINATION WITH ONDANSETRON FOR THE PREVENTION OF DELAYED NAUSEA AND VOMITING INDUCED BY CHEMOTHERAPY

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ABSTRACT

Background The prevention of delayed nausea and vomiting caused by moderately emetogenic chemotherapy for cancer has not been studied systematically.

Methods We enrolled patients who were scheduled to receive chemotherapy for the first time in a double-blind, randomized, multicenter study. All the patients received ondansetron combined with dexamethasone for prophylaxis against emesis that might occur within 24 hours after the start of chemotherapy (acute emesis). They were then divided into two groups: patients who did not have either vomiting or moderate-to-severe nausea (the low-risk group) and patients who had one or both (the high-risk group). Patients in the low-risk group were then randomly assigned to one of the following regimens, given on days 2 through 5 after the start of chemotherapy: oral placebo, 4 mg of dexamethasone given orally twice daily, or 8 mg of ondansetron in combination with 4 mg of dexamethasone, given orally twice daily. Patients in the high-risk group were randomly assigned to receive oral dexamethasone alone or in combination with ondansetron at the same doses as those used in the low-risk group.

Results Among the 618 patients in the low-risk group, there was a complete absence of both delayed vomiting and moderate-to-severe nausea in 91.8 percent of those who received ondansetron combined with dexamethasone, 87.4 percent of those who received dexamethasone alone, and 76.8 percent of those who received placebo. The proportions of patients who were protected by dexamethasone combined with ondansetron or by dexamethasone alone were significantly greater than the proportion protected by placebo ($P < 0.001$ and $P < 0.02$, respectively). Of the 87 patients in the high-risk group, complete protection was achieved in 40.9 percent of those treated with ondansetron and dexamethasone and in 23.3 percent treated with dexamethasone alone (P not significant).

Conclusions The best way to prevent delayed nausea and vomiting in patients receiving moderately emetogenic chemotherapy is to control these complications within the first 24 hours after the start of chemotherapy. Dexamethasone alone provides adequate protection against delayed emesis in patients at low risk (those who have not had acute emesis). (N Engl J Med 2000;342:1554-9.)

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THE administration of moderately emetogenic drugs such as cyclophosphamide, doxorubicin, epirubicin, and carboplatin often causes nausea and vomiting within 24 hours after the start of chemotherapy (acute emesis) or two to five days later (delayed emesis). The combination of a 5-hydroxytryptamine₃-receptor antagonist, such as ondansetron, with dexamethasone can protect 90 percent of patients from acute emesis,^{1,2} but these drugs given alone or in combination protect only 40 to 60 percent of patients from delayed emesis.³⁻⁵ Previous studies of therapy to prevent delayed emesis have not accounted for the possibility that the occurrence of this complication may be influenced by the control of emesis during the first 24 hours.

In the present study, we investigated whether all patients who receive moderately emetogenic chemotherapy need prophylaxis against delayed emesis. We also compared the efficacy of several regimens for the prevention of delayed emesis. Patients receiving chemotherapy for cancer were given prophylaxis against emesis during the first 24 hours and then divided into two groups: those who did not have acute emesis and were therefore at low risk for delayed emesis and those who did have acute emesis and were therefore at high risk for delayed emesis. Patients in these two groups were then randomly assigned to one of three treatments for the prevention of delayed emesis.

METHODS

Patients

From September 1997 to June 1999, all adult patients scheduled to receive moderately emetogenic chemotherapy for the first time at 1 of 23 medical-oncology divisions (22 in Italy and 1 in Yugoslavia) were asked to enter the study. They were to receive cyclophosphamide (600 to 1000 mg per square meter of body-surface area), doxorubicin (≥ 50 mg per square meter), epirubicin (≥ 75 mg per square meter), or carboplatin (≥ 300 mg per square meter), either alone or in combination.

The criteria for exclusion before randomization were the presence of nausea and vomiting or the use of antiemetic agents during the 24 hours before the administration of chemotherapy, a severe concurrent illness other than neoplasia, other causes of vomiting (e.g., gastrointestinal obstruction, central nervous system me-

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tastases, or hypercalcemia), concurrent treatment with glucocorticoids (unless given as supplements) or benzodiazepines (unless given at night for sedation) or abdominal radiotherapy, and a white-cell count of less than 3000 per cubic millimeter or a platelet count of less than 70,000 per cubic millimeter. Also excluded from the study were pregnant women, patients in whom the administration of dexamethasone was contraindicated, patients scheduled to receive highly emetogenic chemotherapy (e.g., dacarbazine, cisplatin, or mechlorethamine) on the same day as moderately emetogenic chemotherapy, and patients scheduled to receive any other cytotoxic agent from day 2 to day 5, with the exception of fluorouracil, etoposide, teniposide, vincristine, vinorelbine, vindesine, and vinblastine.

Design of the Study

Twenty-four hours after the start of moderately emetogenic chemotherapy, patients were divided into two groups according to the effectiveness of prophylaxis against emesis during the first 24 hours: a low-risk group, which included patients who had neither vomiting nor moderate-to-severe nausea within the first 24 hours, and a high-risk group, which included patients who had one or both of these symptoms. The patients in the low-risk group were randomly assigned to receive placebo, dexamethasone, or dexamethasone in combination with ondansetron to prevent delayed nausea and vomiting, and the patients in the high-risk group were randomly assigned to receive dexamethasone or dexamethasone plus ondansetron for this purpose.

Patients and personnel engaged in the study were blinded to the assigned treatment for delayed emesis. The study was approved by the ethics committee of each participating institution; all the patients gave written informed consent. Patients were evaluated according to the intention-to-treat principle.

Antiemetic Therapy

For the prevention of nausea and vomiting during the first 24 hours, all the enrolled patients received a combination of 8 mg of dexamethasone, diluted in 100 ml of saline and administered intravenously over a 15-minute period 30 minutes before the beginning of chemotherapy, and 8 mg of ondansetron, diluted in 100 ml of saline and administered intravenously over a 15-minute period 15 minutes before chemotherapy. In addition, immediately before the start of chemotherapy and then at six-hour intervals, 4 mg of dexamethasone was administered orally, for a total of four doses.

Twenty-four hours after the start of chemotherapy, the patients were randomly assigned to take one of the following regimens of oral antiemetic drugs on days 2 through 5 after chemotherapy. Patients in the low-risk group were to take placebo, 4 mg of dexamethasone twice daily, or the combination of 8 mg of ondansetron and 4 mg of dexamethasone twice daily. Patients in the high-risk group were to take 4 mg of dexamethasone twice daily or the combination of 8 mg of ondansetron and 4 mg of dexamethasone twice daily. A block-balanced randomization list (with 12 patients per block) was used. To ensure that the oral treatment could not be identified, the drugs were put into identical capsules, and each patient received two pill containers. The day after chemotherapy was given, the investigators called each patient to remind him or her of the correct pill containers to be used, according to whether patients were in the high-risk or the low-risk group. Compliance was checked by counting the remaining pills at the end of treatment. Eating was not permitted until six hours after the administration of chemotherapy.

Clinical Assessment

Episodes of nausea and retching or vomiting were recorded by the patients on diary cards for the first 24 hours after chemotherapy (acute emesis) and for the following eight days (delayed emesis). Nausea and vomiting were defined according to previously published criteria.¹

The primary end point of this study was complete protection from both vomiting and moderate-to-severe nausea on days

2 through 5 (complete protection from delayed emesis). The secondary end points were complete protection from delayed vomiting, complete protection from delayed moderate-to-severe nausea, the time to the first episode of acute vomiting, and the mean number of episodes of vomiting on days 2 through 5 among the patients who vomited. Adverse events other than episodes of vomiting or nausea were also recorded on the diary cards by the patients.

Statistical Analysis

In a previous study of patients given moderately emetogenic chemotherapy who did not receive any prophylaxis against delayed emesis, we found that the incidence of delayed vomiting or moderate-to-severe nausea was about 90 percent among patients who had nausea, vomiting, or both during the first 24 hours after the start of chemotherapy and 42 percent among those who did not.⁶ The number of patients to be enrolled in the current trial was calculated as follows. It was assumed that among patients with either vomiting or moderate-to-severe nausea within 24 hours after the start of chemotherapy, prophylaxis with dexamethasone would reduce the incidence of delayed vomiting or nausea from 90 percent to 75 percent when used alone and to 50 percent when combined with ondansetron. To detect a significant difference between these two antiemetic treatments with a probability of 80 percent (with a *P* value of ≤ 0.05 by one-tailed testing defined as indicating statistical significance), 106 patients (53 in each treatment group) would be required. If only 15 percent of enrolled patients had vomiting or moderate-to-severe nausea within the first 24 hours, it would be necessary to enroll at least 706 patients in order to include 106 patients with these symptoms. Therefore, 600 patients who did not have vomiting or moderate-to-severe nausea in the first 24 hours (200 in each treatment group and 200 in a placebo group) would be needed to perform a placebo-controlled evaluation of these treatments for the prevention of delayed emesis. Assuming that the incidence of delayed vomiting or nausea among patients taking placebo is 40 percent, and hypothesizing that this incidence would be reduced to 25 percent with the use of ondansetron combined with dexamethasone (and to 32.5 percent with dexamethasone alone), we estimated the power of the current study to detect a difference between treatment groups to be nearly 90 percent.

Fisher's exact test (two-tailed) was used for the analysis of outcomes in the high-risk group. For the analysis of outcomes in the low-risk group, Fisher's exact test was generalized with use of the Freeman-Halton test⁷ to evaluate the balance of prognostic factors and to compare the proportions with each adverse event or with complete protection from delayed vomiting and moderate-to-severe nausea among the three treatment subgroups. When the difference in proportions was significant, three pairwise comparisons of subgroups were performed, with adjustment of the significance level according to Bonferroni's inequality. Logistic models were used to evaluate the efficacy of the antiemetic treatments in providing complete protection from delayed vomiting and moderate-to-severe nausea, both in a unifactorial analysis and in multifactorial analyses in which all the prognostic factors available on case-record forms were considered; therefore, an overall *G* test and the Wald test for each factor were used.⁸ The 95 percent confidence intervals for the differences between treatment subgroups in the proportions of patients with protection from delayed vomiting and moderate-to-severe nausea were also calculated.

Among the patients who vomited, we compared the mean times to the first episode of vomiting as well as the mean numbers of days with vomiting, moderate-to-severe nausea, or both with the use of nonparametric tests (the Kruskal-Wallis test and Wilcoxon's rank-sum test).

RESULTS

A total of 708 patients entered the study, of whom 1 died and 2 were lost to follow-up. The remaining 705 patients were evaluated according to the intention-to-treat principle. Among these 705 patients

were 5 who refused prophylaxis against delayed emesis because of adverse events during the first 24 hours after the start of chemotherapy and 14 who took the wrong study capsules. The low-risk group consisted of 618 patients who were protected against both vomiting and moderate-to-severe nausea during the first 24 hours. They were randomly assigned to receive placebo (203 patients), dexamethasone (207 patients), or the combination of ondansetron and dexamethasone (208 patients). The high-risk group consisted of 87 patients, all of whom had vomiting, moderate-to-severe nausea, or both within 24 hours after the start of chemotherapy. They were randomly assigned to receive dexamethasone (43 patients) or the combination of ondansetron and dexamethasone (44 patients). The characteristics of the patients were similar in all subgroups within the low-risk and high-risk groups (Table 1).

During the first 24 hours after the start of moderately emetogenic chemotherapy, the standard antiemetic combination of ondansetron and dexametha-

sone completely protected 634 of the 705 patients from vomiting (89.9 percent) and 499 of the 705 patients from any nausea (70.8 percent). These results are similar to those obtained in our previous study.¹ The median time to the first episode of vomiting was 10 hours.

Delayed Nausea and Vomiting

All of the following results were obtained by the evaluation of patients according to the intention-to-treat principle.

In the low-risk group, the efficacy of the combination of ondansetron and dexamethasone was significantly superior to that of placebo according to three measures of complete protection: an absence of both vomiting and moderate-to-severe nausea during days 2 through 5 (protection in 91.8 percent of patients in the dexamethasone-plus-ondansetron subgroup vs. 76.8 percent in the placebo subgroup; $P < 0.001$ for the pairwise comparison with adjustment for Bonferroni's inequality); an absence of vom-

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	LOW-RISK GROUP			HIGH-RISK GROUP	
	PLACEBO (N=203)	DEXA- METHASONE (N=207)	ONDANSETRON PLUS DEXAMETHASONE (N=208)	DEXA- METHASONE (N=43)	ONDANSETRON PLUS DEXAMETHASONE (N=44)
	number of patients (percent)				
Sex					
Male	11 (5.4)	18 (8.7)	8 (3.8)	0	1 (2.3)
Female	192 (94.6)	189 (91.3)	200 (96.2)	43 (100)	43 (97.7)
Age					
<50 yr	82 (40.4)	82 (39.6)	86 (41.3)	29 (67.4)	35 (79.5)
50–64 yr	78 (38.4)	84 (40.6)	76 (36.5)	8 (18.6)	8 (18.2)
≥65 yr	43 (21.2)	41 (19.8)	46 (22.1)	6 (14.0)	1 (2.3)
Median	53	53	51	45	42
Motion sickness					
No	173 (85.2)	179 (86.5)	170 (81.7)	28 (65.1)	32 (72.7)
Yes	30 (14.8)	28 (13.5)	38 (18.3)	15 (34.9)	12 (27.3)
Use of alcohol					
No	161 (79.3)	153 (73.9)	159 (76.4)	40 (93.0)	38 (86.4)
Yes	42 (20.7)	54 (26.1)	49 (23.6)	3 (7.0)	6 (13.6)
Karnofsky score					
≤80	10 (4.9)	17 (8.2)	8 (3.8)	3 (7.0)	3 (6.8)
90 or 100	193 (95.1)	190 (91.8)	200 (96.2)	40 (93.0)	41 (93.2)
Treatment setting					
Outpatient	188 (92.6)	190 (91.8)	197 (94.7)	40 (93.0)	41 (93.2)
Inpatient	15 (7.4)	17 (8.2)	11 (5.3)	3 (7.0)	3 (6.8)
Primary site of tumor					
Breast	189 (93.1)	182 (87.9)	194 (93.3)	42 (97.7)	41 (93.2)
Other	14 (6.9)	25 (12.1)	14 (6.7)	1 (2.3)	3 (6.8)
Chemotherapy					
Cyclophosphamide	105 (51.7)	94 (45.4)	104 (50.0)	9 (20.9)	8 (18.2)
Doxorubicin	43 (21.2)	47 (22.7)	51 (24.5)	15 (34.9)	20 (45.5)
Epirubicin	43 (21.2)	50 (24.2)	42 (20.2)	18 (41.9)	15 (34.1)
Carboplatin	12 (5.9)	16 (7.7)	11 (5.3)	1 (2.3)	1 (2.3)
Full dose of chemotherapy received					
Yes	105 (51.7)	118 (57.0)	110 (52.9)	25 (58.1)	28 (63.6)
No	98 (48.3)	89 (43.0)	98 (47.1)	18 (41.9)	16 (36.4)

*Because of rounding, not all percentages total 100.

iting alone (95.2 percent vs. 87.2 percent, $P < 0.02$); and an absence of moderate-to-severe nausea alone (93.3 percent vs. 81.8 percent, $P < 0.002$) (Table 2). By contrast, dexamethasone alone was significantly better than placebo only in providing protection from both vomiting and moderate-to-severe nausea (protection in 87.4 percent of the patients in the dexamethasone subgroup vs. 76.8 percent in the placebo subgroup; $P < 0.02$). There were no statistically significant differences between ondansetron and dexamethasone in combination and dexamethasone alone in the rate of protection from vomiting, moderate-to-severe nausea, or both vomiting and moderate-to-severe nausea.

Among the patients in the low-risk group who had delayed vomiting or moderate-to-severe nausea, the mean number of days on which these complications occurred did not differ significantly among the three subgroups (2.2 days in the placebo subgroup, 1.9 in the dexamethasone subgroup, and 2.2 in the dexamethasone-plus-ondansetron subgroup). After the prophylaxis against delayed emesis was stopped,

only nine patients in the low-risk group began to vomit again or had moderate-to-severe nausea (eight patients for one day and one patient for two days).

The antiemetic treatment provided much less protection against delayed emesis in the high-risk group than it did in the low-risk group. Among the patients in the high-risk group, all of whom vomited or had moderate-to-severe nausea during the first 24 hours after chemotherapy, the combination of ondansetron and dexamethasone was not significantly more effective than dexamethasone alone in preventing delayed vomiting and moderate-to-severe nausea (Table 3). The delayed complications were prevented in 18 of the 44 patients taking the combination of the two drugs (40.9 percent) and in 10 of the 43 patients taking dexamethasone alone (23.3 percent). Among the patients in the high-risk group who had vomiting or moderate-to-severe nausea, the mean number of days with these complications in the dexamethasone subgroup (2.3 days) was not significantly different from the number of days in the subgroup taking ondansetron plus dexamethasone (2.4).

TABLE 2. RATES OF COMPLETE PROTECTION AGAINST DELAYED VOMITING AND NAUSEA AMONG PATIENTS WHO DID NOT HAVE VOMITING AND MODERATE-TO-SEVERE NAUSEA DURING THE FIRST 24 HOURS AFTER CHEMOTHERAPY.

COMPLETE PROTECTION	DEXAMETHASONE (N=207)	ONDANSETRON PLUS DEXAMETHASONE (N=208)	PLACEBO (N=203)	P VALUE*
Against delayed vomiting and moderate-to-severe nausea	87.4 (82.9–92.0)	91.8 (88.1–95.6)	76.8 (71.0–82.6)	0.001
Difference from placebo	10.6 (3.2–17.9)	15.0 (8.1–21.9)		
Against delayed vomiting	92.3 (88.6–95.9)	95.2 (92.3–98.1)	87.2 (82.6–91.8)	0.02
Difference from placebo	5.1 (0–10.9)	8.0 (2.6–13.4)		
Against delayed moderate-to-severe nausea	89.4 (85.2–93.6)	93.3 (89.9–96.7)	81.8 (76.5–87.1)	0.002
Difference from placebo	7.6 (0.1–14.4)	11.5 (5.2–17.8)		

*P values were calculated by the Freeman–Halton test for the overall comparison among the three subgroups.

TABLE 3. RATES OF COMPLETE PROTECTION AGAINST DELAYED VOMITING AND NAUSEA AMONG PATIENTS WHO HAD VOMITING OR MODERATE-TO-SEVERE NAUSEA DURING THE FIRST 24 HOURS AFTER CHEMOTHERAPY.*

COMPLETE PROTECTION	DEXAMETHASONE (N=43)	ONDANSETRON PLUS DEXAMETHASONE (N=44)	DIFFERENCE	P VALUE†
Against delayed vomiting and moderate-to-severe nausea	23.3 (10.6 to 35.9)	40.9 (26.4 to 55.4)	17.6 (–1.6 to 36.9)	0.11
Against delayed vomiting	46.5 (31.6 to 61.4)	56.8 (42.2 to 71.4)	10.3 (–10.6 to 31.2)	0.40
Against delayed moderate-to-severe nausea	39.5 (24.9 to 54.1)	50.0 (35.2 to 64.8)	10.5 (–10.3 to 31.3)	0.40

*Negative numbers indicate a higher percentage in the group given dexamethasone alone.

†P values were calculated by Fisher’s exact test.

Multifactorial Analyses

Because of the small number of patients in the high-risk group, we found no significant difference between the treatment subgroups with regard to outcome. In the low-risk group, in addition to treatment, only whether or not the full dose of chemotherapy was received had a significant effect. The incidence of delayed emesis was greater among patients who received a full course of chemotherapy than among those who did not ($P < 0.02$) (data not shown). In addition, differences among the chemotherapy regimens had no significant influence on the rate of complete protection from delayed emesis.

Adverse Events

No severe or unexpected adverse events were reported. On days 2 through 5 after the start of chemotherapy, adverse events occurred in 331 (53.6 percent) of the 618 patients who had not had vomiting or moderate-to-severe nausea during the first 24 hours and in 55 (63.2 percent) of the 87 patients who did (P not significant). The most important adverse events are listed in Table 4. Among the patients in the low-risk group, constipation was significantly more frequent among those taking ondansetron and dexamethasone combined (25.0 percent) than among those taking placebo (8.9 percent, $P < 0.001$) or dexamethasone alone (8.7 percent, $P < 0.001$). In the high-risk group, there were no significant differences in the rates of adverse events between the two treatment subgroups.

DISCUSSION

This randomized study shows that the efficacy of prophylaxis against delayed vomiting or moderate-to-severe nausea due to moderately emetogenic chemotherapy for cancer is strongly influenced by the occurrence of these complications during the first 24 hours after the start of chemotherapy. The combination of ondansetron and dexamethasone, which controlled delayed vomiting and nausea in more than 90 percent of patients who did not have these symptoms initially, protected only slightly more than 40 percent of patients who did have vomiting and nausea during the first 24 hours. This finding indicates that an effective way to prevent delayed emesis in patients receiving moderately emetogenic chemotherapy is to control emesis during the first day. The drug combination that we used in this study, a 5-hydroxytryptamine₃-receptor antagonist and dexamethasone, is probably the best choice for preventing acute emesis.¹

Two limitations of our study may hinder the evaluation of antiemetic prophylaxis in the group of patients at high risk for delayed emesis. First, in the high-risk group, we did not include a placebo subgroup. We did this for ethical reasons, because delayed nausea and vomiting would have developed in a high proportion of these patients if they had not been given prophylaxis.⁶ For this reason, we cannot evaluate precisely the benefit conferred by antiemetic prophylaxis in these patients. Second, for unknown reasons, the full course of chemotherapy called for in the protocol was administered to only 386 of the

TABLE 4. ADVERSE EVENTS ON DAYS 2 THROUGH 5 AFTER THE START OF CHEMOTHERAPY.

ADVERSE EVENT	LOW-RISK GROUP				HIGH-RISK GROUP		
	ONDANSETRON PLUS			P VALUE*	ONDANSETRON PLUS		P VALUE†
	DEXAMETHASONE (N=207)	DEXAMETHASONE (N=208)	PLACEBO (N=203)		DEXAMETHASONE (N=43)	DEXAMETHASONE (N=44)	
	no. with events (%)				no. with events (%)		
Headache	7 (3.4)	17 (8.2)	23 (11.3)	0.008	8 (18.6)	10 (22.7)	0.80
Epigastric pain	20 (9.7)	20 (9.6)	13 (6.4)	0.40	5 (11.6)	3 (6.8)	0.49
Rush	25 (12.1)	23 (11.1)	21 (10.3)	0.86	5 (11.6)	4 (9.1)	0.74
Abdominal gas	3 (1.4)	5 (2.4)	4 (2.0)	0.76	1 (2.3)	0	0.50
Constipation	18 (8.7)	52 (25.0)	18 (8.9)	0.001	7 (16.3)	8 (18.2)	1.00
Asthenia	19 (9.2)	23 (11.1)	27 (13.3)	0.42	7 (16.3)	8 (18.2)	1.00
Heartburn	17 (8.2)	15 (7.2)	14 (6.9)	0.87	2 (4.7)	4 (9.1)	0.68
Insomnia	2 (1.0)	10 (4.8)	4 (2.0)	0.06	1 (2.3)	2 (4.5)	1.00
Nervousness	1 (0.5)	4 (1.9)	3 (1.5)	0.41	0	0	1.00
Hot flashes	8 (3.9)	3 (1.4)	3 (1.5)	0.21	1 (2.3)	0	0.50
Vertigo	2 (1.0)	4 (1.9)	5 (2.5)	0.51	3 (7.0)	2 (4.5)	0.68
None	107 (51.7)	91 (43.8)	89 (43.8)	0.18	18 (41.9)	14 (31.8)	0.38

*P values were calculated by the Freeman-Halton test and are for the overall comparison among the three subgroups in the low-risk group.

†P values were calculated by Fisher's exact test and are for the comparison between the two subgroups in the high-risk group.

705 patients (54.8 percent); 37 of these 386 patients (9.6 percent) received less than 90 percent of the dose prescribed in the protocol. As a result of this shortfall and the lower doses for some patients, there were fewer cases of emesis than expected. Therefore, the number of patients in the high-risk group was too small to allow the study to reach a statistical power of 80 percent for detecting a significant difference between outcomes with the two antiemetic treatments (dexamethasone alone or dexamethasone in combination with ondansetron). Given these limitations, the best choice for preventing delayed nausea and vomiting in patients at high risk for these complications remains to be identified.

Among the patients in the low-risk group, both dexamethasone alone and dexamethasone in combination with ondansetron were significantly better than placebo in providing protection against delayed emesis, and no significant difference in efficacy was found between the two regimens. It is noteworthy that high percentages of the patients at low risk who were given placebo did not have delayed vomiting (87.2 percent) or moderate-to-severe nausea (81.8 percent). These percentages are similar to those we found in a previous study of patients who received neither prophylaxis nor placebo against delayed emesis, in which the same regimen for prophylaxis against emesis during the first 24 hours was used. In our opinion, the high rate of protection from delayed emesis among patients who received placebo should not discourage physicians from using antiemetic prophylaxis, especially because an episode of delayed emesis predicts the occurrence of both acute and delayed emesis during subsequent cycles of chemotherapy.⁶ In patients at low risk for delayed nausea and vomiting, dexamethasone alone seems preferable to the combination of dexamethasone and ondansetron because its efficacy is similar to that of the combination, it is better tolerated (specifically, it causes less constipation), and it is less costly.

In conclusion, we believe that prophylaxis against delayed emesis is warranted both in patients at low risk for this complication and in those at high risk, although fewer than half the patients at high risk will be protected and a remarkable number of patients at low risk would be protected without active treatment. Future studies of treatments to prevent delayed emesis must be designed to take into account the influence of complete protection from emesis during the first 24 hours on the control of delayed emesis.⁹

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APPENDIX

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