A Study Evaluating the Efficacy and Tolerability of Tropisetron in Combination with Dexamethasone in the Prevention of Delayed Platinum-Induced Nausea and Emesis

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BACKGROUND. Chemotherapy-induced emesis is one of the most disturbing side effects of cancer therapy. Control of acute emesis has improved substantially during recent years, but control of delayed emesis and nausea remains a challenging problem. The role of 5-HT3 receptor antagonists in the treatment of delayed emesis is disputed.

METHODS. Tropisetron, a highly specific 5-HT3 receptor antagonist, was compared (as an adjunct to dexamethasone) with placebo in a randomized, double blind, multicenter trial for the prevention of delayed emesis during platinum-containing chemotherapy. Three hundred chemotherapy-naive women with gynecologic malignancies were included. The cisplatin dose was in the range of 50–100 mg/m^2.

RESULTS. Acute emesis was prevented completely in 87% of patients and acute nausea in 77% of patients in the complete series. During the complete delayed period (Days 2–6), total control of emesis was achieved in 77% of the dexamethasone and tropisetron-treated patients and in 72% of the patients receiving dexamethasone and placebo ($P = 0.2473$). During the same period nausea was controlled completely in 42% of the dexamethasone and tropisetron group and in 41% of the dexamethasone and placebo group. On Day 3, complete protection from nausea was achieved in 65% of patients receiving tropisetron and in 51% of patients receiving placebo ($P = 0.0304$). Constipation occurred more frequently in the tropisetron group.

CONCLUSIONS. Tropisetron added to dexamethasone improved control of delayed nausea on Day 3 compared with placebo. No significant differences were recorded regarding control of delayed emesis. ***Cancer* 1998;83:1022–32.**
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Nausea and emesis are symptoms frequently associated with cancer chemotherapy. These adverse events generally belong to the category of less well tolerated side effects.[1] The control of nausea and emesis immediately after chemotherapy has improved substantially during recent years and these reactions can be prevented in the majority of patients; however, many individuals still experience nausea and emesis $\geq$ 1 days after chemotherapy.[2]

All patients vomit or experience nausea after the administration of high doses of platinum agents unless antiemetic drugs are given.[3]

High dose metoclopramide cocktails and 5-HT3 receptor antagonists are effective in preventing acute nausea and emesis, but less so with regard to delayed nausea and emesis. The mechanism of action of 5-HT3 receptor antagonists in preventing acute nausea and emesis induced by cancer chemotherapy is likely to involve antagonism of the actions of serotonin at both peripheral and central sites.[4] The mechanisms underlying delayed emesis are not well understood, but they are believed to be different from those involved in acute emesis. The maximum intensity of delayed nausea and emesis normally occurs between 48–72 hours after administration of the chemotherapeutic infusion. Nausea is more frequent than emesis during this period and the intensity is lower, but more protracted, than during the acute phase. The problem of delayed nausea and emesis first was described in patients receiving high dose cisplatin (120 mg/m^2), but delayed symptoms also occur with lower doses of cisplatin and carboplatin, and after the use of cyclophosphamide alone or in combinations.[5,6]

A combination of metoclopramide plus dexamethasone (complete response of 52%) has been shown to be superior to dexamethasone alone (complete response of 35%) or placebo (complete response of 11%) in the prevention of delayed emesis induced by high dose cisplatin.[7]

Ondansetron has been compared with metoclopramide in the prevention of delayed cisplatin-induced nausea and emesis. The efficacy of both drugs was similar in controlling emesis, but metoclopramide was more effective than ondansetron in controlling delayed nausea.[8]

In a large Canadian multicenter study, the value of adding granisetron to dexamethasone versus dexamethasone alone was evaluated for the control of emesis $>$ 24 hours after high dose cisplatin chemotherapy. Complete control of emesis over the complete period was achieved in 38% of patients with the combination and in 35% of patients with dexamethasone alone.[9]

Tropisetron, a selective 5-HT3 receptor antagonist, has shown promising antiemetic properties in the prevention of acute emesis.[10] Tropisetron (5 mg orally once a day) also has been found to be at least as effective as low dose metoclopramide in the prevention of delayed nausea and emesis.[11] In a randomized, double blind, placebo-controlled trial, tropisetron (5 mg orally once a day) plus dexamethasone (4.5 mg orally twice daily on Days 2–6) was found to be superior to tropisetron alone in the prevention of delayed nausea and emesis. The results achieved with this combination were very encouraging after cisplatin chemotherapy.[12] To further evaluate tropisetron in the prevention of delayed, platinum-induced nausea and emesis, a randomized, double blind, placebo-controlled multicenter study was conducted. The primary aim of this study was to evaluate the additional antiemetic effect of orally administered tropisetron compared with placebo when added to dexamethasone during the delayed period (Days 2–6) after platinum-containing chemotherapy.

MATERIALS AND METHODS

Study Design

A randomized, multicenter study in two parallel groups was conducted at five trial centers to compare the clinical efficacy and safety of tropisetron as an adjunct to dexamethasone for antiemetic treatment during platinum-containing chemotherapy. The study was double blind and placebo-controlled. The objective of the study was to evaluate the antiemetic effect during the delayed period (Days 2–6 or 24–144 hours after the start of chemotherapy). During the acute period (Day 1 or 0–24 hours after chemotherapy) all patients received the same type of antiemetic therapy (tropisetron plus dexamethasone). During the delayed period, the patients were randomized to receive dexamethasone plus tropisetron or dexamethasone plus placebo. The patients were randomized before the start of chemotherapy. The study was approved by the Ethics Committees of the five hospitals involved and the National Board of Health when applicable. Informed consent was obtained from all patients.

Patient Selection

Patients with a histologically or cytologically confirmed malignant gynecologic tumor receiving chemotherapy for the first time were entered in the study. All patients received at least 50 mg/m^2 (mean, 54 mg/m^2; range 50–100 mg/m^2) of cisplatin, administered intravenously over a maximum of 2 hours, or carboplatin with dosing according to Calvert's formula (area under the curve = 5–7) on the first day of chemotherapy. Combination with other cytostatic agents (epidoxorubicin, doxorubicin, cyclophosphamide, paclitaxel, teniposide, etoposide, vincristine, and bleomycin) were allowed. The mean dose of epidoxorubicin was 57 mg/m^2 (range, 40–60 mg/m^2), the mean dose of doxorubicin was 46 mg/m^2 (range, 40–50 mg/m^2), and the mean dose of cyclophosphamide was 548 mg/m^2 (range, 500–800 mg/m^2). Paclitaxel, vincristine, and bleomycin were of low emetogenic potential. All agents were administered on the same day (Day 1) of each course of chemotherapy (Table 1). There were no significant differences in the distribution of additional emetogenic agents, in addition to the platinum compounds, in the two random-

TABLE 1
Cytostatic Agents Included in the Regimens Used

	Tropisetron plus dexamethasone	Placebo plus dexamethasone
Agent 1		
Cisplatin	102 (72%)	102 (72%)
Carboplatin	39 (28%)	39 (28%)
Agent 2		
Epidoxorubicin	89 (63%)	77 (55%)
Doxorubicin	22 (16%)	26 (18%)
Cyclophosphamide	23 (16%)	34 (24%)
Paclitaxel	1 (1%)	2 (1%)
Teniposide	5 (4%)	1 (1%)
Vincristine	1 (1%)	0 (0%)
Bleomycin	0 (0%)	1 (1%)
Agent 3		
Cyclophosphamide	119 (84%)	131 (93%)
Vincristine	18 (13%)	5 (4%)
Etoposide	0 (0%)	5 (4%)
Bleomycin	4 (3%)	0 (0%)
Courses no.		
1	80 (57%)	74 (52%)
2	61 (43%)	67 (48%)

TABLE 2
Characteristics of the Randomized Treatment Groups

	Tropisetron plus dexamethasone	Placebo plus dexamethasone
No. of patients	141	141
Females	141 (100%)	141 (100%)
Males	0 (0%)	0 (0%)
Mean age (yrs)	61.4	59.6
Mean weight (kg)	67.8	68.5
Mean height (cm)	164	163
History of alcohol use	58 (41%)	62 (44%)
Alcohol consumption g/week	20.4	24.2
History of motion sickness	24 (17%)	22 (16%)
History of nausea of pregnancy	51 (36%)	31 (22%)
Ovarian carcinoma	101 (72%)	102 (72%)
Endometrial carcinoma	24 (17%)	29 (21%)
Cervical carcinoma	8 (6%)	5 (4%)
Fallopian tube carcinoma	7 (5%)	3 (2%)
Other cancinomas	1 (1%)	2 (1%)

ized treatment groups. Patients were scheduled to be evaluated during two identical courses of chemotherapy. Patients with nausea or emesis prior to the start of chemotherapy were not included. Treatment of nausea and emesis with drugs other than the study medication was not permitted, except when the patients fulfilled the criteria of treatment failure.

Study Population

The study population was comprised of 300 chemotherapy-naive women scheduled to receive at least 2 courses of a platinum-containing chemotherapy regimen. The patients, comprised of patients with various gynecologic carcinoma diagnoses, were recruited consecutively at five different gynecologic oncology departments in Sweden. The period of recruitment was from January 1, 1995 to June 30, 1996. Of the enrolled patients, 150 were allocated to the dexamethasone plus tropisetron treatment group and 150 to the dexamethasone plus placebo group. Randomization was performed before the start of any type of chemotherapy.

The ages of the patients ranged from 22–86 years, with a mean age of 60.4 years. There were no statistically significant differences between the treatment groups with respect to age, weight, or height. A history of alcohol intake also was recorded as well as a history of motion sickness and pregnancy- associated nausea. Additional characteristics of the treatment groups are given in Table 2.

Of the enrolled 300 patients, 282 were evaluable with regard to the efficacy parameters. Protocol violations were recorded for 17 patients regarding the antiemetic treatment administered. They were excluded from the assessments of treatment efficacy but were included in the safety analyses.

Antiemetic Treatments

Tropisetron (Navoban®; Novartis Pharma Ltd., Basel, Switzerland) was given on Day 1 as 5 mg in 100 mL of normal saline administered intravenously over 15 minutes at the end of the prehydration period (i.e., immediately before the start of the platinum infusion). On Days 2–6 each patient received a 5-mg tropisetron capsule or a similar placebo capsule in the morning immediately after awakening. The 5-mg dose was chosen on the basis of prior dose-finding studies conducted with tropisetron using a wide dose range of 5–100 mg per day. These studies did not demonstrate any therapeutic benefit for doses $>$ than 5 mg per day, but most likely showed higher rates of side effects. The hypothesis was that 5 mg of tropisetron was sufficient to block the 5-HT3 receptors for at least 24 hours. Eating and drinking were not allowed during the next 2 hours.

Dexamethasone (from the hospital pharmacies) was administered on Day 1 as 20 mg administered intravenously over 10 minutes at the end of the prehydration period (i.e., immediately before the start of the platinum infusion). On Days 2–6 the patients received 3 mg of dexamethasone orally twice daily.

Rescue Therapy

Rescue therapy was allowed in cases of treatment failure. During the first 24 hours, intravenous meto-

clopramide (3 mg/kg) was used. During the delayed period (24–144 hours), metoclopramide (10 mg) was given orally three times daily as rescue treatment.

Assessment of Efficacy

Nausea and emesis were recorded by a research nurse on a "nursing chart" on the case report form during hospitalization and by the patient on a diary card at home. All patients were hospitalized for at least 24 hours (during the acute emetic phase) and the recordings made by the research nurse always were completed before the patient left the hospital. Records were kept for the 6 consecutive days after the platinum infusion in each course. Emesis and retching were recorded as separate events. The presence of nausea was recorded every 12 hours within 24-hour periods. Nausea was assessed as present or absent, by duration (hours), and in three degrees of intensity (slight, moderate, and severe). The acute phase (first 24 hours) as well as the delayed phase (24–144 hours) also were assessed by the Visual Analogue Scale (VAS) (0–100 mm) instrument as a global measurement of satisfaction with the antiemetic treatment. Rescue treatment was recorded per 24-hour period.

Endpoints of Efficacy

Total control of emesis was defined as no events of emesis or retching within a 24-hour period. Major control was defined as one to two events of emesis or retching. Minor control was defined as three to four events of emesis or retching. Five or more events within a 24-hour period were defined as no control of emesis (treatment failure). Total control of nausea was defined as no episodes of nausea, major control as slight nausea, minor control as moderate nausea, and no control as severe nausea within a 24-hour period. The first 24 hours after the start of chemotherapy was defined as Day 1 (the acute period). Days 2–6 (24–144 hours) were defined as the delayed period. Nausea and emesis during the first 24 hours after the platinum infusion was termed "acute." When nausea and emesis started after that period, it was termed "delayed."

Safety Assessment

Against the background of the symptoms of the underlying disease and the side effects originating from the platinum-containing chemotherapy, it was difficult to identify the adverse events associated with the antiemetics. Therefore, and to be able to compare the two antiemetic regimens, safety information from all available sources was taken into account (i.e., conventionally reported adverse events, unusual symptoms reported by the patient on the diary cards, electrocardiograms, data on vital signs, and laboratory values).

All adverse events were classified as severe or nonsevere (a combination of adverse events graded as mild or moderate). A systolic blood pressure $>$ 170 mm Hg, a diastolic blood pressure $>$ 100 mm Hg, a body temperature $>$ 38.0 °C, and a radial pulse $>$ 120 beats per minute were classified as abnormal. The most abnormal value for each patient (if any) was selected from all the readings taken during a course. Laboratory data were recorded at screening and at the end of each chemotherapy course to identify clinically relevant influences of the antiemetic treatments on hematologic and biochemical parameters. Values outside clinically relevant ranges were classified as abnormal. An abnormality in vital signs and laboratory values was classified as newly occurring if all previous values were normal.

Specific questions concerning headache, constipation, edema, and insomnia were asked every 12 hours on Days 1–6 in the diary.

Statistical Methods

All statistical tests for the comparison of treatment groups are presented with two-sided P values. Comparisons between treatment groups were made using Pearson's chi-square test and Fisher's exact test, when necessary, for discrete variables, the Student's t test for normally distributed continuous variables, and the Mann-Whitney U test for continuous variables that were not distributed normally. Ninety-five percent confidence intervals (95% CI) for the average responses were derived for each treatment group using a normal approximation to the binomial distribution. Total control of nausea and emesis on Day 1, Days 2–6 combined, and on all separate days was assessed in Course 1 and Course 2. A logistic regression analysis also was used to evaluate significant prognostic factors with regard to the control of nausea on Day 3 of the delayed phase.

RESULTS

Control of Nausea and Emesis on Day 1 (acute period)

During the first 24 hours all patients in both groups received the same type of antiemetic treatment (tropisetron plus dexamethasone). Total control of emesis during this period was achieved in 87% of patients (95% CI, 84–91%). During the same period of time in Course 2, the percentage of total control of emesis was 89% (95% CI, 84–95%). The percentages of acute control were similar in the two randomized treatment groups. Total control of emesis ranged between 75% and 90% in cisplatin-treated patients when analyzed by the trial center. These differences were not statistically significant (Pearson's chi-square: 3.9005; P = 0.4197).

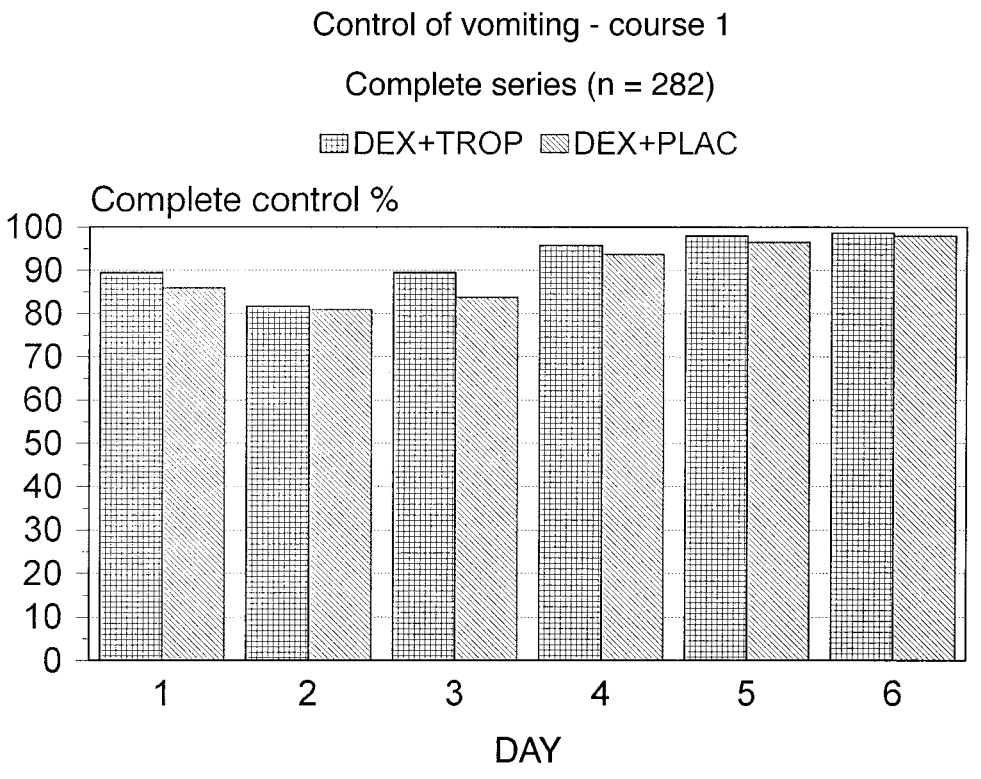

FIGURE 1. The frequency of complete control of emesis during Course 1 of chemotherapy, Days 1–6. There was no statistically significant difference in the efficacy of the two antiemetic treatments. DEX: dexamethasone; TROP: tropisetron; PLAC: placebo.

Nausea was prevented completely in 77% (95% CI, 73–83%) in the complete series during the first 24 hours of Course 1. The percentages of acute control were similar in the two randomized treatment groups. In Course 2, acute nausea was prevented in 74% (95% CI, 67–82%) in the complete series. Total control of nausea ranged from 50–76% for cisplatin-treated patients in the different trial centers. These differences were not statistically significant (Pearson's chi-square: 6.0669; $P = 0.1942$).

The global assessment of treatment satisfaction during the first 24 hours by the VAS instrument (mean, 8 mm; 95% CI, 6–10 mm) showed no significant ($P = 0.9251$) differences for the 2 randomized groups.

Control of Nausea and Emesis on Days 2–6 (delayed period)

The total control rate of emesis increased from 82% on Day 2 to 99% on Day 6 in the dexamethasone plus tropisetron group and from 81% to 98% in the dexamethasone plus placebo group (Fig. 1). No statistically significant differences were recorded on any one of these days. During the complete delayed period, total protection from emesis was achieved in 77% of the patients treated with dexamethasone plus tropisetron and in 72% of the patients treated with dexamethasone plus placebo (Pearson's chi-square: 0.6714; $P = 0.4126$)(Table 3). The range of variation between trial centers for the complete delayed period was 60–78% when both treatment groups were combined (Pearson's chi-square: 5.4153; $P = 0.2473$).

The total control rate of nausea increased from 56% on Day 2 to 85% on Day 6 in the dexamethasone plus tropisetron group and from 54% to 81% in the dexamethasone plus placebo group. On Day 3, the frequency of complete protection from nausea was 65% in the dexamethasone plus tropisetron group and 52% in the dexamethasone plus placebo group. This difference was statistically significant in the complete series (cisplatin and carboplatin patients combined) (Pearson's chi-square: 4.6869; $P = 0.0304$)(Fig. 2). The assessment of control of nausea on Day 3 was refined further by logistic regression analysis. Control of acute nausea (Day 1), type of platinum agent (cisplatin or carboplatin), age, and tropisetron or placebo were all independent and significant prognostic factors. During the complete delayed period (Days 2–6), nausea was controlled completely in 42% of patients in the dexamethasone plus tropisetron group and in 41% of patients in the dexamethasone plus placebo group. This difference was not statistically significant (Pearson's chi-square: 0.0700; $P = 0.7913$)(Table 4). The range of variation between trial centers for the complete delayed period was 17–31% when both treatment groups were combined (Pearson's chi-square: 3.3037; $P = 0.5084$). During Course 2, delayed nausea (Days

TABLE 3
Frequency of Patients With Total, Major, Minor, or No Control of Emesis (Treatment Failure) during the Delayed Period (Days 2–6) of Courses 1 and 2 of Chemotherapy

	Tropisetron plus dexamethasone	Placebo plus dexamethasone
Course 1		
No. of patients	141	141
Control of emesis[a]		
Total	108 (77%)	102 (72%)
Major	22 (16%)	24 (17%)
Minor	3 (2%)	6 (4%)
Treatment failure	8 (6%)	9 (6%)
95% CI		
Total (%)	[70–84]	[65–80]
Total or major (%)	[88–97]	[84–94]
Course 2		
No. of patients	64	68
Control of emesis[a]		
Total	58 (91%)	56 (82%)
Major	6 (9%)	6 (9%)
Minor	0 (0%)	5 (7%)
Treatment failure	0 (0%)	1 (1%)
95% CI		
Total (%)	[84–98]	[73–91]
Total or major (%)	[100–100]	[84–98]

95% CI: 95% confidence interval.

[a] Total = no episodes of emesis, major = 1–2 episodes of emesis, minor = 3–4 episodes of emesis, treatment failure = ≥ 5 episodes of emesis.

Confidence intervals for the proportion of patients with total and either total or major control are based on a normal approximation to the binomial distribution.

2–6) was completely controlled in 45% of patients in the dexamethasone plus tropisetron group and in 48% of patients in the dexamethasone plus placebo group (Pearson's chi-square: 0.1533; $P = 0.6954$).

The global assessment of treatment satisfaction during the delayed period by the VAS instrument (mean, 16 mm; 95% CI, 13–19 mm) showed no significant ($P = 0.1736$) differences for the 2 randomized groups (dexamethasone plus tropisetron: mean, 14 mm; dexamethasone plus placebo: mean, 18 mm).

Cisplatin and Carboplatin Series

In the cisplatin series (n = 206), acute emesis was prevented completely in 86% of all patients. Delayed emesis (Days 2–6) was prevented completely in 69% of patients in the dexamethasone plus tropisetron group and in 68% of patients in the dexamethasone plus placebo group. No statistically significant differences were recorded (Pearson's chi-square: 0.0031; $P = 0.9559$). Acute nausea was prevented completely in 74% of all cisplatin-treated patients. Delayed nausea (Days 2–6) was prevented completely in 30% of patients in the dexamethasone plus tropisetron group and in 34% of patients in the dexamethasone plus placebo group. No significant differences were recorded (Pearson's chi-square: 0.4298; $P = 0.5121$). The analyses were performed in the first course of chemotherapy.

In the carboplatin series (n = 76) acute emesis was prevented completely in 92% of all patients. Delayed emesis (Days 2–6) was prevented completely in 97% of patients in the dexamethasone plus tropisetron group and in 84% of patients in the dexamethasone plus placebo group. This difference was statistically significant (Pearson's chi-square: 4.2319; $P = 0.0397$). Acute nausea was prevented fully in 88% of all patients. Delayed nausea was prevented completely in 87% of patients in the dexamethasone plus tropisetron group and in 65% of patients in the dexamethasone plus placebo group on Day 2 (Pearson's chi-square: 5.2307; $P = 0.0222$), and in 90% and 72%, respectively, on Day 3 (Pearson's chi-square: 3.7854; $P = 0.0517$). During the complete delayed period (Days 2–6), nausea was prevented in 74% of patients in the dexamethasone plus tropisetron group and in 60% of patients in the dexamethasone plus placebo group (Pearson's chi-square: 1.7355; $P = 0.1877$). The analyses were performed in chemotherapy Course 1.

Nausea and Emesis versus Cisplatin Dose

Two dose levels of cisplatin, 50 mg/m^2 and 75 mg/m^2, were analyzed. During the acute period, emesis was prevented in 85% of patients at both dose levels. During the delayed period, a significant (Pearson's chi-square: 7.2414; $P = 0.0071$) difference was noted on Day 2, with 80% complete protection at the 50 mg/m^2 dose and 58% at the 75 mg/m^2 dose. The protection rates during Days 3–5 also were higher in the 50 mg/m^2 dose group, but the differences were not statistically significant. During the complete delayed period (Days 2–6), the control rates for the 50 mg/m^2 and the 75 mg/m^2 dose level groups were 72% and 45%, respectively (Pearson's chi-square: 9.0856; $P = 0.0026$).

Acute nausea was prevented in 73% of patients at the 50 mg/m^2 dose and in 76% of patients at the 75 mg/m^2 dose (Pearson's chi-square: 0.1288; $P = 0.7197$). The total control rates during the delayed period for the 50 mg/m^2 and 75 mg/m^2 dose levels were 32% and 27%, respectively. These differences were not statistically significant (Pearson's chi-square: 0.2527; $P = 0.6152$). Higher dose levels of cisplatin could not be analyzed due to the small number of patients treated with doses > 75 mg/m^2.

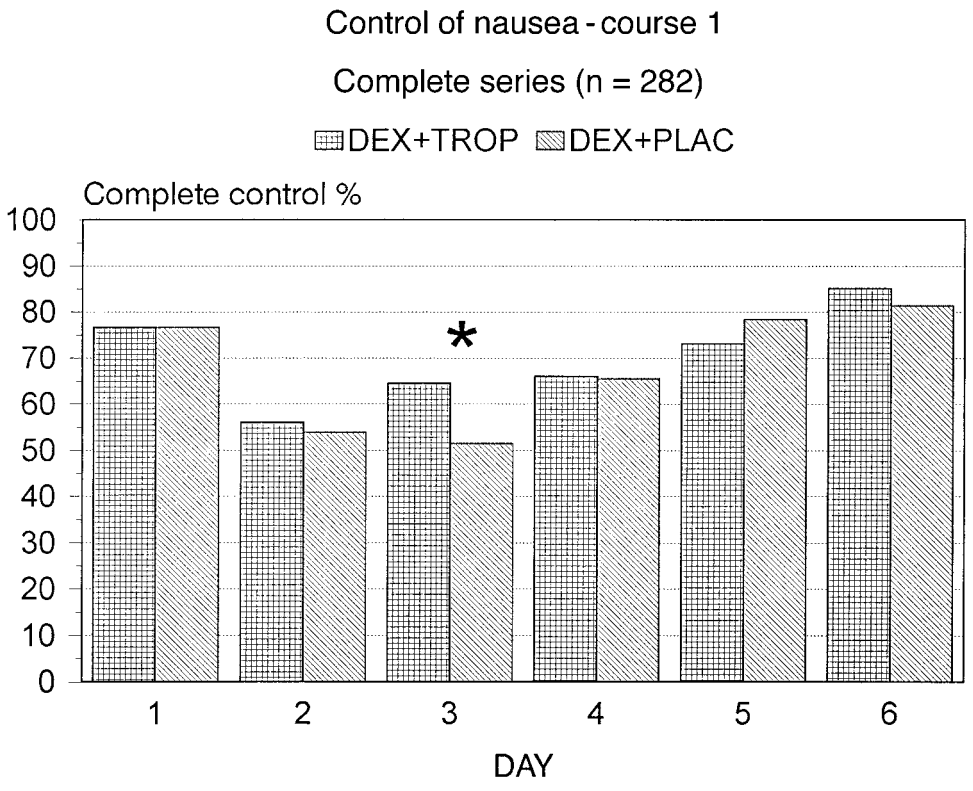

FIGURE 2. The frequency of complete control of nausea during Course 1 of chemotherapy, Days 1–6. The dexamethasone plus tropisetron combination (DEX + TROP) was significantly (*) ($P = 0.0304$) more efficacious than dexamethasone plus placebo (DEX + PLAC) on Day 3. There were no significant differences between the two regimens during the complete delayed period (Days 2–6).

Control of Delayed Nausea and Emesis versus Acute Control

In the group of patients with complete control of nausea and emesis during the first 24 hours (n = 214), delayed emesis was controlled completely in 83% of patients (n = 177) and nausea in 53% of patients (n = 113). This was highly significantly ($P < 0.0001$) different from the results in patients (n = 67) in whom nausea and emesis were not controlled completely during the acute phase. In the latter group, delayed emesis was controlled completely in 48% of patients (n = 32) and delayed nausea in only 4% of patients (n = 3). The efficacy ratings of dexamethasone plus tropisetron and dexamethasone plus placebo were similar when assessed within these two groups. The only exception was control of delayed nausea on Day 3 in patients not protected fully from nausea and emesis during the first 24 hours, during which time tropisetron (complete control in 39% of patients) was superior to placebo (complete control in 12% of patients) (Pearson's chi-square: 6.4178; $P = 0.0113$).

Rescue Treatment

Thirty-three of 283 evaluable patients (12%) in the complete series received rescue treatment at some point during Days 1–6 in the first course of chemotherapy. Thirteen patients (9%) in the tropisetron group received rescue medication, and rescue therapy was given to 20 patients (13%) in the placebo group. This difference was not statistically significant (Pearson's chi-square: 1.6253; $P = 0.2024$). The specific day of rescue treatment and the total number of days patients received rescue medication also were similar in the two randomized groups.

Adverse Effects

In general, the two antiemetic regimens were well tolerated. Some type of adverse event was recorded in 75% of patients in the dexamethasone plus tropisetron group and in 82% of patients in the dexamethasone plus placebo group. This difference was not statistically significant (Pearson's chi-square: 2.1662; $P = 0.1411$). The majority of the reported adverse events were related to the malignant disease or the chemotherapy. Adverse events occurring with a frequency of $> 5\%$ or recorded as severe are shown in Table 5. Adverse events most likely associated with the antiemetic agents were headache, constipation, edema, and insomnia. The only significant difference in adverse events was related to constipation, which was significantly (Pearson's chi-square: 11.2258; $P = 0.0008$) more frequent in the dexamethasone plus tropisetron group (58%) than in the dexamethasone plus

TABLE 4
Frequency of Patients with Total, Major, Minor, or No Control of Nausea (Treatment Failure) during the Delayed Period (Days 2–6) of Courses 1 and 2 of Chemotherapy

	Tropisetron plus dexamethasone	Placebo plus dexamethasone
Course 1		
No. of patients	141	140
Control of nausea[a]		
Total	58 (41%)	54 (39%)
Major	48 (34%)	41 (29%)
Minor	27 (19%)	32 (23%)
Treatment failure	8 (6%)	13 (9%)
95% CI		
Total (%)	[33–49]	[31–47]
Total or major (%)	[68–82]	[60–76]
Course 2		
No. of patients	60	68
Control of nausea[a]		
Total	24 (40%)	32 (47%)
Major	22 (37%)	20 (29%)
Minor	11 (18%)	11 (16%)
Treatment failure	3 (5%)	5 (7%)
95% CI		
Total (%)	[28–52]	[35–59]
Total or major (%)	[66–87]	[66–87]

95% CI: 95% confidence interval.

[a] Total = no nausea, major = slight nausea, minor = moderate nausea, treatment failure = severe nausea.

Confidence intervals for the proportion of patients with total and either total or major control are based on a normal approximation to the binomial distribution.

TABLE 5
No. of Patients with Adverse Events

Side effect	Tropisetron plus dexamethasone (n = 150) No. (%)	Placebo plus dexamethasone (n = 150) No. (%)	P value
Headache	54 (36.0)	65 (43.3)	NS
Constipation	87 (58.0)	58 (38.7)	<0.001[a]
Insomnia	73 (48.7)	74 (49.3)	NS
Edema	13 (8.7)	24 (16.0)	NS
Sedation	10 (6.7)	8 (5.3)	NS
Dizziness	4 (2.7)	4 (2.7)	NS
Abdominal pain	3 (2.0)	3 (2.0)	NS
Other	18 (12.0)	23 (15.3)	NS
Total	112 (74.7)	120 (80.0)	

NS: nonsignificant difference ($P > 0.05$).

[a] Highly significant difference.

placebo group (39%). No other significant differences were recorded.

DISCUSSION

Delayed nausea and emesis remain a significant problem in cancer chemotherapy. According to an arbitrary definition, nausea and emesis occurring > 24 hours after the chemotherapy infusion are designated as delayed nausea and emesis.[2] The pattern of nausea and emesis varies with different chemotherapeutic agents and combinations of such agents. Cisplatin is the typical agent inducing delayed emesis. A biphasic pattern of emesis is postulated for this drug.[13]

Delayed emesis after cisplatin infusion has been studied most thoroughly,[7–9,11,12,14,15] but a number of articles also have addressed the problem of moderately emetogenic chemotherapy (anthracyclines, cyclophosphamide, teniposide, 5-fluorouracil, and methotrexate).[16–19] The mechanisms underlying delayed emesis are not well understood, but they are believed to be different from those involved in acute emesis. Both the previously available antiemetics and the new 5-HT3 receptor antagonists are less effective during the delayed phase than during the acute period (the first 24 hours). Mechanisms not involving 5-HT3 receptors are believed to be involved. No universally accepted experimental models have been available.[20,21] Recently, two animal models using the ferret[21] and the piglet[22,23] have been presented. However, these models may not exactly reflect the 5-HT3 effectiveness in man, and therefore their future status as standard models is questionable.

In 1989 Kris et al. demonstrated in a double blind randomized study that a combination of metoclopramide plus dexamethasone (complete response of 52%) was superior to dexamethasone alone (complete response of 35%) and placebo (complete response of 11%) in the prevention of delayed emesis induced by high dose cisplatin. In delayed nausea, both metoclopramide plus dexamethasone and dexamethasone were significantly superior to placebo.[7] In a study by de Mulder et al. published in 1990, ondansetron was compared with metoclopramide in the prevention of delayed cisplatin-induced nausea and emesis. For the control of emesis, the two drugs were similarly efficacious, but for delayed nausea, metoclopramide had superior efficacy. However, patients appeared to prefer ondansetron, most likely because of the spectrum of side effects.[8]

In a large American multicenter study (538 chemotherapy-naive patients who received ≥ 70 mg/m^2 of cisplatin), patients who received ondansetron had significantly fewer emetic episodes on Days 2–5 than those who received placebo ($P < 0.002$). Patients who received ondansetron had significantly less nausea on Days 2–3. The control of delayed nausea and emesis was most notable during the 2 days immediately after cisplatin adminstration.[24]

Granisetron has been found to be active in acute (Day 1) and late (Days 5–7) phases of cisplatin-induced nausea and emesis. However, it was found to be less effective during Days 2–4. A triphasic pattern was postulated for emesis resulting from cisplatin use and a non-5-HT3 receptor-mediated mechanism during the middle period could explain the inferior control of emesis.[15] In a large Canadian multicenter study, the value of adding granisetron to dexamethasone versus dexamethasone alone was assessed for control of emesis > 24 hours after high dose cisplatin chemotherapy. In the study, 434 patients were randomized to receive granisetron, 1 mg orally, once daily in combination with dexamethasone, 8 mg orally, twice daily for 6 days or dexamethasone alone for the same period. Complete control of emesis over the 7-day period was achieved in 38% of patients receiving the combination and in 35% of patients receiving dexamethasone alone ($P = 0.532$). The control of nausea for the complete 7-day period was achieved in 28% versus 25% in the 2 groups and the mean nausea severity over the same interval did not differ significantly. The authors concluded that the effectiveness of dexamethasone was not augmented by the addition of granisetron.[9]

Lofters et al. found no significant difference between ondansetron and dolasetron in the prevention of delayed emesis after moderately emetogenic chemotherapy, but the addition of dexamethasone significantly improved the efficacy of both drugs over the studied 7-day period.[25]

Tropisetron has been found to be as effective as low dose metoclopramide in the prevention of delayed nausea and emesis.[11] In a double blind, randomized, placebo-controlled trial, tropisetron plus dexamethasone was found to be superior to tropisetron alone in the prevention of delayed nausea and emesis. There was a striking difference with regard to complete control, especially in the prevention of delayed nausea, on Days 2–3 in favor of the corticosteroid-treated patients.[12]

In the current study, we investigated the effect of adding a standard dose of tropisetron (5 mg) to a baseline corticosteroid treatment during the delayed period (Days 2–6). The trial was randomized, double blind, and placebo-controlled. All patients received the same type of antiemetic treatment during the first 24 hours (tropisetron plus dexamethasone). Background characteristics and acute control of nausea and emesis were well balanced between the two randomized groups. The antiemetic agents were given orally during the delayed period. Our design was similar to that of the Canadian study comparing granisetron plus dexamethasone with dexamethasone alone.[9] No significant differences were observed in the complete control of emesis in the 2 groups on any of the days studied during the delayed period or for the complete delayed period (77% and 72%, respectively). This was true of both the first and the second course of chemotherapy. Delayed nausea was controlled at a lower rate compared with emesis. During Day 3 (48–72 hours after chemotherapy), the combination of tropisetron plus dexamethasone (complete control rate of 65%) was superior to placebo plus dexamethasone (complete control rate of 52%) in the prevention of nausea in the complete series, in the carboplatin subgroup, and in those patients in whom complete control of nausea and emesis was not achieved during the first 24 hours. Complete protection during Days 2–6 was achieved in 42% of patients in the dexamethasone plus tropisetron group and in 41% of patients in the dexamethasone plus placebo group. This difference was not statistically significant. A separate analysis of a shorter delayed period (24–96 hours) also did not show any significant difference. The overall ratings of treatment satisfaction during the acute and delayed periods were similar for the two treatment groups. The need for rescue therapy also was similar in the two groups. In the carboplatin subgroup, delayed nausea during Days 2–3 and during the complete delayed period (Days 2–6) was completely controlled in significantly more patients when tropisetron was added to dexamethasone. This most likely is explained by a more prolonged phase of acute emesis for carboplatin compared with cisplatin.[26]

Both treatment regimens were well tolerated and no serious side effects were recorded. Constipation was significantly more frequent in the group treated with tropisetron on Days 1–6 compared with the group that received tropisetron on Day 1 only. The same observation was made by Olver et al. regarding ondansetron versus placebo.[27] The absolute frequencies of adverse events were high in both groups, but this most likely is explained by the technique used for recording side effects (direct questions [e.g., concerning headache, constipation, edema, and insomnia every 12 hours], and using a patient diary). The method used for collecting data on side effects significantly influences the absolute frequencies recorded according to our experience in prior antiemetic studies.[10–12,19]

The conclusions drawn from this study are the following: 1) a combination of tropisetron and dexamethasone is highly effective in the prevention of acute platinum-induced nausea and emesis; 2) dexamethasone alone is as effective as a combination of dexamethasone plus tropisetron in the prevention of delayed emesis; 3) tropisetron appears to

enhance the efficacy of dexamethasone in the control of nausea on Day 3 in cisplatin-treated patients, and on Days 2–3 (as well as for the complete delayed period) in carboplatin-treated patients; 4) acute control of nausea and emesis, type of platinum agent (cisplatin vs. carboplatin), age of the patient, and the addition of tropisetron are significant prognostic factors for the control of nausea 48–72 hours after the initiation of chemotherapy; 5) the frequency of constipation increases significantly when tropisetron is added to dexamethasone during the delayed period, whereas other types of side effects are not reinforced; 6) further research still is needed to determine the optimal antiemetic therapy for delayed platinum-induced nausea. New strategies for treatment[28] and new antiemetic agents with other mechanisms of action[29,30] are needed to further improve the control of delayed nausea and emesis.

REFERENCES

1. Coates A, Abraham S, Kaye SB, Sowerbutte T, Frewin C, Fox RM, et al. On the receiving end-patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983;19:203–8.
2. Kris MG, Gralla RJ, Clark RA, Tyson LB, O'Connell JP, Wertheim MS, 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.
3. Gralla RJ, Itri LM, Pisko SE, Anna E, Squillante RN, Kelsen DP, 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* 1981;305:905–9.
4. Andrews PLR, Davis CJ, Bingham S, Davidson HIM, Hawthorn J, Maskell L. The abdominal visceral innervation and the emetic reflex: pathways, pharmacology, and plasticity. *Can J Physiol Pharmacol* 1990;68:325–45.
5. Cubeddu LX, Hoffman IS, Fuenmayor NT, Finn AL. Antagonism of serotonin S3 receptors with ondansetron prevents nausea and emesis induced by cyclophosphamide-containing chemotherapy regimens. *J Clin Oncol* 1990;8:1721–7.
6. Kaizer L, Warr D, Hoskins P, Latreille J, Lofters W, Yau J, et al. Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: a phase III trial by the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1994;12:1050–7.
7. 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.
8. De Mulder PHM, Seynaeve C, Vermorken JB, van Liessum PA, Mols-Jevdevic S, Allman EL, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. *Ann Intern Med* 1990;113:834–40.
9. Johnston D, Latreille J, Laberge F, Stewart D, Rusthoven J, Findlay B, et al. Preventing nausea and vomiting during days 2–7 following high dose cisplatin chemotherapy. A study by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) [abstract 1745]. *Proc Am Soc Clin Oncol* 1995;14:529.
10. Leibundgut U, Lancranjan I. First results with ICS 205–930 (5-HT3 receptor antagonist) in prevention of chemotherapy-induced emesis. *Lancet* 1987;I:1198.
11. Sorbe B, Högberg T, Glimelius B, Schmidt M, Wernstedt L, Hansen O, et al. A randomized, multicenter study comparing the efficacy and tolerability of tropisetron, a new 5-HT3 receptor antagonist, with a metoclopramide-containing antiemetic cocktail in the prevention of cisplatin-induced emesis. *Cancer* 1994;73:445–54.
12. Sorbe B, Högberg T, Himmelmann A, Schmidt M, Räisänen I, Stockmeyer M, et al. Efficacy and tolerability of tropisetron in comparison with a combination of tropisetron and dexamethasone in the control of nausea and vomiting induced by cisplatin-containing chemotherapy. *Eur J Cancer* 1994;30A:629–34.
13. Kris MG, Pisters KMW, Hinkley L. Delayed emesis following anticancer chemotherapy. *Support Care Cancer* 1994;2:297–300.
14. Olver I, Paska W, Depierre A, Seitz JF, Stewart DJ, Goedhals L, et al. A multicentre, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. *Ann Oncol* 1996;7:945–52.
15. Smyth J. Delayed emesis after high-dose cisplatin: the residual problem. Presented at Proceedings of the European Society of Medical Oncology, Lyon, France, November 8, 1992.
16. Jones AL, Hill AS, Soukop M, Hutcheon AW, Cassidy J, Kaye SB, et al. Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 1991;338:483–7.
17. Beck TM. The pattern of emesis following high-dose cyclophosphamide and antiemetic efficacy of ondansetron. *Anticancer Drugs* 1995;6:237–42.
18. Roila F, Ballatori E, de Angelis V, Tonato M, Riva E, Panza MT, et al. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *N Engl J Med* 1995;332:1–5.
19. Sorbe B, Andersson H, Schmidt M, Söderberg M, Högberg T, Wernstedt L, et al. Tropisetron (Navoban) in the prevention of chemotherapy-induced nausea and vomiting: the Nordic experience. *Support Care Cancer* 1994;2(6):393–9.
20. Florczyk AP, Schurig JE, Bradner WT. Cisplatin-induced emesis in the ferret: a new animal model. *Cancer Treat Rep* 1982;66:187–9.
21. Rudd JA, Jordan CC, Naylor RJ. Profiles of emetic action of cisplatin in the ferret: a potential model of acute and delayed emesis. *Eur J Pharmacol* 1994;262:R1–2.
22. Grélot L, Stunff HL, Milano S, Blower PR, Romain D. Repeated administration of the 5-HT3 receptor antagonist granisetron reduces the incidence of delayed cisplatin-induced emesis in the piglet. *J Pharmacol Exp Ther* 1996;279:255–61.
23. Milano S, Blower P, Romain D, Grélot L. The piglet as a suitable animal model for studying the delayed phase of cisplatin-induced emesis. *J Pharmacol Exp Ther* 1995;274:951–61.

24. Navari RM, Madajewicz S, Anderson N, Tchekmedyian NS, Whaley W, Garewal H, 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.
25. Lofters WS, Pater JL, Zee B, Dempsey E, Walde D, Moquin J-P, et al. Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy. *J Clin Oncol* 1998;15:2966–73.
26. Ossi M, Anderson E, Freeman A. 5-HT3 receptor antagonists in the control of cisplatin-induced delayed emesis. *Oncology* 1996;53:78–85.
27. Olver I, Paska W, Depierre A, Seitz JF, Stewart DJ, Goedhals L, et al. A multicentre, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. *Ann Oncol* 1996;7:945–52.
28. 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; 53:86–91.
29. Rudd JA, Jordan CC, Naylor RJ. The action of the NK1 tachykinin receptor antagonist , CP 99,994, in antagonizing the acute and delayed emesis induced by cisplatin in the ferret. *Br J Pharmacol* 1996;119:931–6.
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.