



Randomised trial for the prevention of delayed emesis in patients receiving high-dose cisplatin

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Summary Despite recent advances in control of acute emesis following cisplatin-based chemotherapy regimens, delayed emesis remains a significant cause of treatment-related morbidity and factors associated with delayed emesis have not yet been evaluated. A prospective randomised trial was conducted to compare the efficacy and toxicity of granisetron, dexamethasone plus prochlorperazine with granisetron alone in controlling cisplatin-induced delayed emesis and to identify the important factors that influence its occurrence and severity. Seventy cisplatin-naïve patients with inoperable solid tumors participated in the trial. Patients who received 80 mg m⁻² or 100 mg m⁻² of cisplatin were randomly assigned to receive either granisetron 40 µg kg⁻¹ intravenously (i.v.) on day 1, dexamethasone 20 mg i.v. on days 2 and 3 and prochlorperazine 5 mg orally thrice daily on days 1–5 or granisetron 40 µg kg⁻¹ i.v. on day 1 alone. There was no difference in their acute antiemetic efficacy. A combination regimen was more effective than granisetron alone in preventing delayed symptoms, with superior rates of complete plus major responses of 77% vs 51% ($P = 0.0460$). Treatment arm was the only determinant factor for the occurrence of delayed emesis ($P = 0.0101$).

Keywords: delayed emesis; cisplatin; dexamethasone; granisetron, prochlorperazine

Nausea and vomiting are among the most common and feared side-effects of cancer chemotherapy. In particular, cisplatin has been recognised for its high emetogenic potential (Von Hoff *et al.*, 1979). The quality of life of the cancer patients and their compliance with treatment, which continues over several courses, depend on the effective management of these side-effects. It is very important to achieve good control during the first course of chemotherapy in order to avoid anticipatory nausea and vomiting before the next or subsequent treatments.

In recent years significant advances in control of acute emesis during the initial 24 h after cisplatin administration have been made, using high-dose metoclopramide (Gralla *et al.*, 1981), dexamethasone (Kris *et al.*, 1983, 1985a) and 5-hydroxytryptamine (5-HT₃) antagonists (Cunningham *et al.*, 1987; Hainsworth and Hesketh, 1992; Jantunen *et al.*, 1993; Joss *et al.*, 1993). However, the success obtained in the prevention of acute emesis has not been extended to control of delayed emesis induced by cisplatin. Delayed emesis appearing beyond the first 24 h after chemotherapy remains a significant cause of treatment-related morbidity and patient refusal of further chemotherapy despite the use of various antiemetic drugs, including corticosteroids, major tranquilisers, and 5-HT₃ antagonists. The treatment of choice for delayed emesis still remains to be established; in fact, only a few randomised trials have been carried out. The factors associated with delayed emesis have also not been sufficiently studied. Therefore, we carried out an open randomised study to compare the efficacy and safety of a combination of granisetron, dexamethasone and prochlorperazine with granisetron alone in the prophylaxis of delayed emesis, and to define the factors associated with delayed symptoms induced by cisplatin in patients who had not previously received cisplatin-based chemotherapy.

Patients and methods

Patient selection

Eligibility criteria for entry into the study were as follows: (1) histological diagnosis of malignant tumours; (2) cisplatin

doses of ≥ 80 mg m⁻²; (3) age < 80 years; (4) performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (5) adequate bone marrow function (leucocyte count ≥ 4000 µl⁻¹, platelet count $\geq 100\,000$ µl⁻¹ and haemoglobin ≥ 9 g dl⁻¹), adequate hepatic function (bilirubin ≤ 1.5 mg dl⁻¹, transaminases \leq twice the upper limit of normal) and adequate renal function (creatinine ≤ 1.4 mg dl⁻¹, 24 h creatinine clearance ≥ 60 ml min⁻¹); (6) no presence of nausea and/or vomiting before the cisplatin treatment; (7) no prior cisplatin-containing chemotherapy; (8) no current use of corticosteroids; (9) no new change of doses of major tranquilisers or sleeping pills habitually used (prochlorperazine should not be habitually used); (10) no evidence of severe uncontrollable diabetes; (11) no evidence of brain metastasis or brain tumors; (12) no medical problems severe enough to prevent compliance with the protocol; and (13) written informed consent.

Treatment protocol

After eligibility criteria were ascertained, patients were randomly assigned to receive either granisetron alone (arm 1) or granisetron, dexamethasone, and prochlorperazine (arm 2). All patients received a single high dose of cisplatin (80 mg m⁻² or 100 mg m⁻²) for the first time in combination with other chemotherapeutic agents consisting of 6–9 mg m⁻² of vindesine, 8 mg m⁻² of mitomycin C, or 300 mg m⁻² of etoposide. They also received 40 µg kg⁻¹ of granisetron intravenously (i.v.) 15 min before cisplatin administration was given as a single i.v. infusion on day 1. Patients assigned to treatment arm 1 received no preventive antiemetics except granisetron on day 1, and patients allocated to treatment arm 2 received 20 mg of dexamethasone i.v. on days 2 and 3, and 5 mg tablets of prochlorperazine orally three times (30 min before breakfast, lunch and dinner) on days 1–5. If more than two episodes of severe nausea or vomiting were observed, patients received a standard dose (10 mg per body i.v. or intramuscularly; i.m.) of metoclopramide.

Definition of response

Following the cisplatin administration, each patient was monitored by direct observation, patient interviews and bedside self-assessment. An emetic episode was defined as either an episode of vomiting or retching. We attempted to assess

other parameters including nausea and appetite loss. The primary efficacy parameter was the number of emetic episodes. Nausea and food intake assessment were used as secondary parameters in evaluating the efficacy. The number of episodes of vomiting and severity of nausea was recorded during each 24 h period for 5 days after cisplatin administration. Each patient was asked to count the number of emetic episodes during each interval. The duration and severity of nausea were rated by patients, for the same intervals, on categorical descriptive scales that were divided into two grades. The baseline assessment of food intake was obtained immediately before cisplatin administration. The level of appetite was checked at each meal for 5 days. The categories on scales of emetic episodes, nausea and appetite loss are as follows. Responses for vomiting and retching are graded as complete control (no emetic episodes), grade 0; major control (1–2 emetic episodes), grade 1; failure (\geq three emetic episodes), grade 2. Responses for nausea were also recorded according to two graded scales by patients as no or mild nausea, good control; moderate or severe nausea, failure. Food intake was assessed by four graded scales as being: as usual, grade 0; half of the usual, grade 1; one-third of the usual, grade 2; less than one-third of the usual, grade 3. They were recorded every day on days 2–5 and the worst day analysis was performed. The criteria of the worst day analysis for delayed emesis were as follows: complete control, the absence of nausea, vomiting and retching; major control, grade 1 emetic episodes or grade 0 emetic episode with mild nausea; and others were classified as failure.

Evaluation for toxicities

Toxicities were classified using World Health Organization criteria (World Health Organization, 1979). Other adverse effects, which have no grading in the WHO criteria, were classified as follows: grade 0, no symptom; grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, extremely severe and/or life-threatening.

Statistical analysis

Analyses of nausea and emetic episodes were performed separately for day 1 (acute emesis) and days 2–5 (delayed emesis).

This trial was planned to include 62 patients to provide of more than 80% power to detect at the 5% level a 30% increase in overall control of delayed emesis from the anticipated 50% in the granisetron alone group.

Chi-square test or Fisher's exact test was used to compare response rates of the worst day analysis as well as to evaluate

the imbalance of factors between the two groups. The statistical significance of differences in the distribution of the age was determined using paired, two-tailed Student's *t*-test. The Mann–Whitney *U*-test was used to compare daily grades of emetic episodes and nausea between two treatment groups. Multivariate analysis of prognostic variables for response was carried out using a logistic regression model. All *P*-values refer to a two-sided significance test, and a *P*-value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Between April 1993 and January 1995, a total of 70 patients were entered into the study and all were eligible. Sixty-eight patients had lung cancer and two had colon cancer with lung metastases. Both groups of patients (granisetron alone vs granisetron, dexamethasone plus prochlorperazine) were well matched for age, sex, performance status and daily alcohol consumption (75 g or more) (Table I).

Acute nausea

Patterns and the severity of acute nausea between the two groups did not differ. The rates of no or mild nausea observed during the first 24 h were 69% in a combination of granisetron, dexamethasone and prochlorperazine, and 54% in a granisetron-alone group ($P = 0.3267$).

Acute emetic episodes

The rates of complete emetic control were 51% in arm 1 and 66% in the 2 ($P = 0.3318$). The rates of complete plus major emetic control were similar, with 72% in treatment arm 1 vs 77% in treatment arm 2 on day 1 ($P = 0.7845$). A variety of factors were analysed to determine their impact on the control of acute emesis. Gender and a habitual high alcohol intake (≥ 75 g per day) were significant for controlling acute emesis and *P*-values were 0.0043 and 0.0161 respectively. A multivariate analysis showed that gender was the only significant factor for control of acute emesis among six factors ($P = 0.0044$).

Delayed nausea

The rates of no or mild nausea were 43% in arm 1 and 74% in arm 2 on day 2 ($P = 0.0153$), and on day 3, 54% in arm 1 and 72% in arm 2 ($P = 0.2162$). Three patients only experienced most severe nausea after day 3.

Table I Patients characteristics

	Arm 1	Arm 2	P-value
No. of patients	35	35	
Gender: Male/Female	26/9	28/7	0.7759
Median age (range)	63 (37–75)	63 (41–75)	0.8412
Histological type			
Lung cancer			
NSCLC	29	27	
SCLC	4	8	0.1842
Colon cancer	2	0	
Performance status (ECOG)			
0, 1/2	22/13	25/10	0.6103
Chest irradiation: Yes/No	5/30	11/24	0.1547
Habitual alcohol intake			
High/Low	8/27	5/30	0.5387
Chemotherapeutic regimen			
PV	9	12	
MVP	22	17	0.4796
PE	4	6	

NSCLC, non-small-cell lung carcinoma; SCLC, small-cell lung carcinoma; PV, cisplatin 100 mg m⁻² + vindesine 3 mg m⁻²; MVP, cisplatin 80 mg m⁻² + mitomycin 8 mg m⁻² + vindesine 3 mg m⁻²; PE, cisplatin 80 mg m⁻² + etoposide 100 mg m⁻² × 3 days. Habitual high alcohol intake, ≥ 75 g daily.

Delayed emetic episodes

The rates of complete plus major control were 63% in treatment arm 1 and 86% in arm 2 on day 2 ($P = 0.0450$). Almost all of the patients experienced the worst vomiting episodes on day 2 or day 3 in both of the treatment arms, and then the number of emetic episodes declined.

Duration of nausea and vomiting

Eighteen (51%) patients experienced nausea for 4 or more days on arm 1 and nine (26%) on the 2 arm and four (11%) and five (14%) patients experienced 4 or more days of emetic episodes respectively.

Worst day analysis for delayed emesis

Complete plus major control rates for delayed emesis were 51% (95% confidence interval, 34–69%) in the granisetron alone group and 77% (95% confidence interval, 60–90%) in the combination therapy group; the difference was statistically significant ($P = 0.0460$). Nine potential factors for the control of delayed emesis were analysed in univariate analysis (Table II). Presence of prior non-cisplatin chemotherapy, simultaneous chest irradiation, and performance status were not important factors determining the incidence of emetic episodes. Gender was also not a significant factor on an

overall control rate, but significant for complete control ($P = 0.0077$). A habitual high alcohol intake and good control of acute emesis were significant factors, indicating a good protection from delayed emesis. In this trial, all habitual high alcohol users were men. When patients were divided into the three groups of women, men without a habitual high alcohol intake and men with a habitual high alcohol intake, the control rates were 50%, 61% and 92% respectively ($P = 0.0482$).

Multivariate logistic regression analysis of variables, including age, performance status, gender, concurrent chest irradiation, presence of non-cisplatin containing prior therapy, level of acute emesis and habitual alcohol intake for protection from delayed emesis was carried out (Table III). Treatment arm ($P = 0.0101$) was only of independent prognostic significance for attaining a major control of delayed emetic episodes.

Safety

There were no differences in toxicity during the trial between the two arms. Headache is known to be the most common adverse event in patients receiving 5-HT₃-blockers. In our study, five patients (7%) experienced grade 1 headache, but needed no treatment. Six patients (9%) experienced constipation on day 1. Dexamethasone plus prochlorperazine for control of delayed emesis was extremely well tolerated by

Table II Response rate for delayed emesis according to prognostic factor

	No. of patients	Complete control ^a	Major control ^b	Response %	P-value
Arm					
1	35	7	11	18 (51)	0.0460
2	35	10	17	27 (77)	
Gender					
Male	54	17*	20	37 (69)	0.2888
Female	16	0*	8	8 (50)	
Age (years)					
≥64	32	10	13	12 (92)	0.3342
<64	38	7	15	33 (58)	
PS (ECOG)					
0, 1	47	12	17	29 (62)	0.7044
2	23	5	11	16 (70)	
Habitual alcohol intake					
≥75 g daily	13	10**	2	12 (92)	0.0242
<75 g daily	57	7**	26	33 (58)	
Prior therapy					
Yes	29	5	12	17 (59)	0.5628
No	41	12	16	28 (68)	
CDDP dose (mg m ⁻²)					
80	49	10	20	30 (61)	0.5862
100	21	7	8	15 (71)	
Chest irradiation					
Yes	16	5	5	10 (63)	0.6604
No	54	12	23	35 (65)	
Response for acute emesis					
Responder	52	16	22	38 (73)	0.0201
Non-responder	18	1	6	7 (39)	

^aComplete control (experienced no nausea and no emetic episode). ^bMajor control (experienced 0 emetic episode with any nausea or 1–2 emetic episodes), * $P = 0.0077$; ** $P < 0.0001$.

Table III Multivariate analysis of variables for delayed emesis

Parameters	Odds ratio	95% Confidence Interval	P-value
Arm	0.2065	0.0576	0.6555
Habitual high alcohol intake	0.1130	0.0053	0.8287
Control of acute emesis	2.7548	0.6973	11.7835
Chest irradiation	0.3859	0.0694	1.9029
Dose of CDDP	2.3404	0.4725	13.6819
Age	1.3813	0.4080	4.7214
Prior therapy	1.4051	0.3622	5.7327
Performance status	1.2026	0.3366	4.4046
Gender	0.8326	0.1817	3.8903

patients, and no major drug-related adverse effects (more than grade 1) were observed. No patient experienced dystonic reactions, somnolence, extrapyramidal symptom and sedation. Two patients (3%) experienced grade 1 face rash. These adverse effects were mild, transient and easily tolerable.

Discussion

The 5-HT₃ antagonists have improved the treatment of acute cisplatin-induced nausea and vomiting. Chevallier (1993) reported the trial comparing granisetron alone with high-dose metoclopramide plus dexamethasone, showing that no significant differences were detected between the two groups in the incidence of acute emesis induced by cisplatin. The incidence of delayed emesis induced by cisplatin was reported to be 50–70% when 5-HT₃ antagonists were used to control acute emesis (Gandara *et al.*, 1992; Italian Group for Antiemetic Research, 1993; Kaizer *et al.*, 1994). In contrast to the success in the protection from acute emesis, the 5-HT₃ antagonists seem to be less effective against delayed emetic symptoms (Kaye *et al.*, 1992). Several antiemetics including dexamethasone, minor tranquilisers and selective dopamine D₂ antagonists, which may have different mechanisms of actions, have been reported effective in the control of delayed emesis (Hamik and Peroutka, 1989; Kris *et al.*, 1989; Louvet *et al.*, 1991; Moreno *et al.*, 1992; Herrstedt *et al.*, 1993). Dexamethasone has improved the antiemetic effect of a 5-HT₃ antagonist in patients receiving cisplatin-based chemotherapy. Combined use of these agents seems more effective in the control of delayed emesis than any single drug alone. Based on these data, this randomised study compared the three-drug combination of a 5-HT₃ antagonist granisetron, dexamethasone and prochlorperazine with the treatment with granisetron alone in the prevention of delayed nausea and vomiting in patients receiving cisplatin-containing regimens, demonstrating the apparent advantage for overall control of delayed emesis of combination therapy over granisetron alone (77% in the combination group vs 51% in the granisetron alone; $P = 0.0460$) (Table II). There was a statistically significant 26% difference in the complete and major control rates between the two arms.

In agreement with other investigators (Kris *et al.*, 1985b, 1989; Gandara *et al.*, 1992), the highest incidence of delayed

emesis was observed on day 2 after cisplatin administration, and only three patients experienced first delayed emesis on day 4 or later in our study. Delayed emesis seems to become a smaller problem if it is well controlled on days 2 and 3. Therefore, every effort should be directed to obtaining perfect protection from both acute and delayed emesis on days 1–3.

Dose of cisplatin, control of acute emesis and gender have previously been reported as important determinants for delayed emesis (Kris *et al.*, 1985a; Roila *et al.*, 1991; Italian Group for Antiemetic Research 1994). In this study, dose of cisplatin (80 mg m⁻² or 100 mg m⁻²) was also not a significant factor. This may be because all patients received high-dose cisplatin (either dose level of 80 mg m⁻² or 100 mg m⁻²) (Table II). Treatment arm, habitual high alcohol intake and control of acute emesis were significant variables in univariate analysis. Multivariate analysis using logistic regression models revealed that treatment arm (arm 1 or arm 2) was the only important factor ($P = 0.0101$) (Table III). A habitual high alcohol intake was the second, but did not reach statistical significance. The importance of complete control of acute emesis, which is often quoted as a significant determinant of subsequent antiemetic control, was not confirmed by multivariate analysis. This may be explained by different characteristics of population in this study, or by the relatively small number of patients, which provides only a low statistical power for detecting differences of moderate magnitude between the groups.

In conclusion, a combination of granisetron, dexamethasone and prochlorperazine was more effective than granisetron alone in protection from delayed emesis after high-dose cisplatin. Since 23% of patients treated with the combination regimen suffered from severe delayed emesis, further studies with other more effective combinations of antiemetics with different mechanisms of action are needed to improve results in this population.

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