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Short Communication

Randomised Double-blind Study Comparing Tropisetron Alone and in Combination with Dexamethasone in the Prevention of Acute and Delayed Cisplatin-induced Emesis

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In a randomised, double-blind and parallel-design multicentre study, 282 chemotherapy-naive cancer patients received tropisetron 5 mg intravenously (i.v.) before high-dose cisplatin on day 1, and oral tropisetron 5 mg daily on days 2–6, in combination with either placebo ($n = 143$) or dexamethasone ($n = 135$), given i.v. on day 1 and orally on days 2–6. Complete protection from acute vomiting/nausea was achieved in 76.3%/79.3% of patients receiving the combination and in 55.2%/61.5% of those receiving tropisetron alone. Complete protection on days 2–6 from delayed vomiting/nausea was obtained in 60%/60% and 39.2%/40.6%, respectively. Tropisetron in combination with dexamethasone is safe and more effective than tropisetron alone in the prevention of both acute and delayed cisplatin-induced emesis. © **1998 Elsevier Science Ltd.**

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INTRODUCTION

THE SUCCESSFUL control of nausea and vomiting induced by high-dose cisplatin is a difficult aim in daily patient care. The introduction of serotonin 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist has represented an important advance, especially for prevention of acute emesis [1, 2]. Tropisetron is a selective 5-HT$_3$ antagonist that prevents emesis due to cisplatin [3]. The present study was undertaken to evaluate whether the addition of dexamethasone can improve the efficacy of tropisetron in the control of both acute and delayed cisplatin-induced emesis.

PATIENTS AND METHODS

A multicentre, randomised, double-blind, placebo-controlled and parallel-group design was used.

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Patient selection

From November 1992 to February 1994, adult chemotherapy-naive cancer patients who received cisplatin at doses ≥ 50 mg/m^2, were enrolled into the study. Cisplatin was administered only on the first day of treatment, either alone or in combination with other chemotherapeutic agents. On days 2–6, either no chemotherapy or only agents with low emetic potential were administered: 5-fluorouracil, bleomycin and etoposide.

Anti-emetic treatment

The first treatment consisted of 5 mg of tropisetron intravenous (i.v.) and 20 mg of dexamethasone i.v., before cisplatin on day 1. On days 2–6, the patients received oral tropisetron, 5 mg daily in the morning, plus oral dexamethasone, 8 mg twice daily on days 2 and 3, and 4 mg twice daily on days 4–6. The second treatment consisted of tropisetron at the same dose and schedule as the first treatment group. In addition, the patients received placebo i.v. on day 1, and placebo tablets on days 2–6, that were taken according to the same schedule as dexamethasone in the first

Table 1. *Patients' characteristics*

	Tropisetron plus placebo *n* (%)	Tropisetron plus dexamethasone *n* (%)
Number of patients	143	135
Sex		
Male	119 (83)	109 (81)
Female	24 (17)	26 (19)
Age (years)		
Mean	58	57
Range	19–77	20–78
Primary cancer		
Lung	59 (41)	57 (42)
Head and neck	40 (28)	37 (27)
Ovary	14 (10)	19 (14)
Oesophageal	13 (9)	10 (7)
Other	17 (12)	12 (9)
Cisplatin dose (mg/m^2)		
50–75	26 (18)	29 (21)
76–99	21 (15)	17 (13)
≥ 100	96 (67)	89 (66)
Mean dose	91 mg/m^2	92 mg/m^2
Administration of chemotherapy with low emetic potential on days 2–6		
Yes	66 (46)	55 (41)
No	77 (54)	80 (59)
Treatment setting		
Outpatient	29 (20)	33 (24)
Inpatient	114 (80)	102 (76)
Alcohol consumption (g/day)		
None or < 100	109 (76)	113 (84)
≥ 100	31 (22)	18 (13)
Unknown	3 (2)	4 (3)
Mean	41 g/day	36 g/day

regimen.

Clinical assessment and statistical analysis

The number of emetic episodes and the intensity of nausea were studied for acute emesis (first 24 h after chemotherapy) and delayed emesis (days 2–6). The categories of responses for emetic episodes were: complete protection (absence of emetic episodes), major protection (one or two episodes in 24 h) and failure (more than five episodes per day). Nausea was graded using the following scale: none, mild (did not interfere with normal daily life), moderate (interfered with normal daily life) and severe (patients bedridden due to nausea). Patients experiencing treatment failure were considered as failures for the remaining study days.

Chi square and Fisher's exact tests were used to compare nausea and vomiting between treatment groups. Quantitative variables (age, alcohol and cisplatin dose) were compared by means of Mann–Whitney's U-test.

RESULTS

A total of 282 patients were included in the study. Four patients were not evaluable: two were lost to follow-up, one was unable to swallow due to oesophageal cancer, and one used benzodiazepines. The characteristics of the 278 assessable patients are listed in Table 1. The groups were compared at baseline, and no significant differences in their characteristics were found. Efficacy data on acute nausea and vomiting are listed in Table 2. Patients in the group receiving tropisetron plus dexamethasone had higher complete protection rates from acute vomiting, nausea and both nausea and vomiting than patients in the tropisetron–placebo group.

The proportions of overall complete protection against delayed vomiting, nausea and nausea and vomiting were higher for patients who received the combination than for those who received tropisetron alone (Table 2). The analysis of delayed emesis for each day of the study showed that complete protection from vomiting, nausea and both on days 2 and 3 (as well as the proportion with complete protection from vomiting on day 5) was significantly higher in the tropisetron–dexamethasone group than in the tropisetron group. On the other days, the efficacy of the two treatments did not differ significantly. In the subgroup of patients who did not receive any chemotherapy on days 2–6, the rates of complete protection from delayed nausea and vomiting were significantly higher only for the combination treatment group on day 2 (data not shown).

Overall data for days 1–6 showed a significantly higher proportion of complete protection from vomiting, nausea and both nausea and vomiting in the tropisetron plus dexamethasone group (54.1%, 57% and 47.4%) than in the single drug group (30.1%, 36.4% and 19.6%).

The most frequently reported adverse events were constipation (20%), headache (18%), diarrhoea (7%) and epigastric pain (8%). Both anti-emetic regimens were well

Table 2. *Anti-emetic efficacy on acute and delayed nausea and vomiting*

	Tropisetron plus placebo ($n = 143$) % of patients (95% confidence interval)	Tropisetron plus dexamethasone ($n = 135$) % of patients (95% confidence interval)	
Acute emesis			
Complete protection from vomiting	55.2 (47.1–63.4)	76.3 (69.1–83.5)	0.0002
Complete protection from nausea	61.5 (53.6–69.5)	79.3 (72.4–86.1)	0.001
Complete protection from both vomiting and nausea	46.2 (38.0–54.3)	71.1 (63.5–78.8)	0.0002
Treatment failure	10.5 (5.5–15.5)	7.4 (3.6–13.2)	0.37
Delayed emesis (days 2–6)			
Complete protection from vomiting	39.2 (31.2–47.2)	60.0 (51.7–68.3)	0.0005
Complete protection from nausea	40.6 (32.5–48.6)	60.0 (51.7–68.3)	0.001
Complete protection from both vomiting and nausea	26.6 (19.3–33.8)	51.1 (42.7–59.5)	0.0001
Treatment failure	3.9	3.0	0.32

tolerated and no difference in the type or frequency of adverse events between the two groups was observed, except for hiccups, which were more frequent in the tropisetron plus dexamethasone group (4.4% versus 0.7%), and asthenia, which was more common in the tropisetron alone group (9.1 versus 3).

DISCUSSION

Previous trials have studied the combination of the 5-HT_3 antagonists ondansetron [4, 5] and granisetron [6, 7] with dexamethasone in the prophylaxis of acute emesis caused by cisplatin, showing that the combination of both drugs is more effective than the 5-HT_3 antagonist alone. The addition of dexamethasone to tropisetron has improved the control of emesis in patients with prior poor protection to tropisetron alone [8, 9]. In the present trial, the addition of dexamethasone to tropisetron significantly enhanced the rates of complete protection from cisplatin-induced acute nausea, vomiting and total control when compared with tropisetron alone. The mean dose of cisplatin administered in the study was greater than that used in many studies. Our results combined with previously reported trials support the conclusion that 5-HT_3 antagonists should be routinely used in combination with dexamethasone to maximise the effect against acute emesis due to cisplatin.

However, delayed emesis remains an unsolved problem [10]. As the results of our study show, delayed emesis is now more frequent than acute emesis, although it is usually less severe. To date, there is no really effective treatment for the control of delayed nausea and vomiting. Dexamethasone or metoclopramide alone are of little value [11]. The combination of both is superior to either dexamethasone alone or placebo [11, 12], and is widely used. Ondansetron alone has a significant but limited activity in the prevention of delayed emesis [13], and a recently reported study showed a similar efficacy of ondansetron plus dexamethasone and metoclopramide plus dexamethasone [14]. In our study, the combination of tropisetron and dexamethasone on the first and subsequent days gave significant protection against delayed emesis. One possibility is that the benefit of the first day dexamethasone dose on acute emesis could have also contributed to the control of delayed emesis, assuming a possible influence of acute emesis on delayed emesis. In conclusion, our study revealed that dexamethasone maintained for the acute and delayed period of vomiting did not add notable toxicity to tropisetron alone, and it improved markedly the control of both acute and delayed emesis. Further studies to optimise the control of delayed emesis are warranted.

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