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Aims and Scope

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Randomised comparison of ondansetron plus dexamethasone with dexamethasone alone for the control of delayed cisplatin-induced emesis

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Abstract

The role of 5-hydroxytryptamine$_3$ (HT_3) antagonists in the treatment of delayed emesis is still controversial. To evaluate whether 5-HT_3 antagonists can add to the efficacy of corticosteroids in controlling delayed emesis, we performed a randomised, prospective, open study comparing ondansetron plus dexamethasone with dexamethasone alone in cisplatin-treated patients. 149 cisplatin-naïve patients with lung cancer received at least 60 mg/m^2 of cisplatin and were treated with dexamethasone 32 mg intravenously (i.v.) and granisetron 3 mg i.v. on day 1. Patients were randomly assigned to receive either dexamethasone 16 mg i.v. alone (arm A) or dexamethasone plus ondansetron 8 mg daily (arm B) on days 2–4. None of the efficacy variables related to control of delayed emesis differed significantly between the two arms. In conclusion, there does not appear to be sufficient evidence to support the prolonged use of 5-HT_3 receptor antagonists after 24 h of cisplatin-containing chemotherapy. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Delayed emesis; Antiemetics; Cisplatin; Ondansetron; Dexamethasone; 5-HT_3-receptor antagonists

1. Introduction

Nausea and emesis are among the most distressing adverse effects of cancer chemotherapy. The control of nausea and emesis has a remarkable effect on the patient's quality of life and willingness to complete their course of treatment.

Acute emesis after cisplatin administration has been widely studied, and following the introduction of 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonists, significant advances have been made in its control [1–4]. Furthermore, large multicentre randomised trials have shown that the combination of a 5-HT_3 receptor antagonist plus a corticosteroid is significantly more effective than a 5-HT_3 antagonist alone. In these trials, the combination of a 5-HT_3 receptor antagonist plus a corticosteroid has been shown to yield an approximately 75% (range 58–96%) complete control rate of acute emesis after a high-dose cisplatin-based regimen [5–9].

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However, the success achieved in the prevention of acute emesis has not been extended to the control of the delayed emesis induced by cisplatin. Delayed emesis, although less intense than acute emesis, is still a major problem for many patients, and its incidence varies, but can be as high as 80% [10,11]. Since the neuropharmacological mechanism of delayed emesis is not well understood, prevention of this problem has been based on empirical results [12]. In the clinical practice guidelines developed by the American Society of Clinical Oncology (ASCO), a corticosteroid plus metoclopramide or a 5-HT_3 antagonist is recommended for the prevention of delayed emesis [12]. Although the combination of corticosteroid and metoclopramide has been shown to be superior to placebo, and also to dexamethasone alone [11,13], it is controversial whether continuation of a 5-HT_3 antagonist after acute control of emesis prevents the development or reduces the frequency of delayed emesis [14–20,23].

To evaluate the role of a 5-HT_3 antagonist, in particular oral ondansetron, in the prevention of delayed emesis, we planned a single-institution randomised, prospective, open study comparing ondansetron plus

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dexamethasone with dexamethasone alone in cisplatin-treated patients.

2. Patients and methods

2.1. Patient selection

Eligibility criteria included pathologically-confirmed lung cancer, age between 15 and 80 years, performance status of 3 or less according to the Eastern Cooperative Oncology Group (ECOG) scale and chemotherapy including cisplatin at a dose of at least 60 mg/m^2. Patients meeting any of the following criteria were excluded: primary brain tumour or symptomatic brain metastases, prior treatment with cisplatin, presence of nausea and/or vomiting before the cisplatin treatment, current use of corticosteroids, recent changes in the doses of major tranquilisers or sleeping pills habitually used, clinically significant gastrointestinal disease, or evidence of severe uncontrollable diabetes. Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of our hospital.

2.2. Treatment protocol

Patients were randomly assigned to receive either dexamethasone alone (arm A) or dexamethasone plus ondansetron (arm B). All the patients received cisplatin treatment (60 or 80 mg/m^2) only on the first day (day 1) of treatment, either alone or in combination with other chemotherapeutic agents. On days 2–4, either no chemotherapy or only agents with low emetogenicity were administered. On day 1, patients received prophylactic treatment with granisetron 3 mg intravenously (i.v.) and dexamethasone 32 mg i.v. in four separate doses (8 mg each). Then patients assigned to treatment arm A received dexamethasone 8 mg i.v. twice daily on days 2–4. The treatment for arm B consisted of oral ondansetron 8 mg daily in the morning on days 2–4, in addition to dexamethasone at the same dose and on the same schedule as arm A. If more than two episodes of severe nausea or vomiting were observed, patients received a standard dose of metoclopramide (10 mg per body i.v. or intramuscularly) or domperidone (60 mg per body suppository). Requirement of any other antiemetic treatment necessitated withdrawal from the study.

2.3. Assessment of efficacy

The protocol-specified primary end-points were complete control of emesis (CCE), defined as no emetic episodes, no use of rescue medication, and no missing data during the 4-day period; complete control of nausea (CCN), defined as no nausea, no use of rescue medication, and no missing data during the 4-day period; and total control of emesis (TCE), defined as no vomiting, no nausea, no use of rescue medication, and no missing data during the 4-day period.

Immediately after randomisation (baseline period) and at the end of each day (days 1–4), all patients were asked to complete a daily diary. These diaries consisted of the number of emetic episodes, the intensity of nausea, their assessment of global satisfaction with the antiemetic treatment, and general mood at that time. Since all the patients were inpatients over the 4-day study period, monitoring by direct observation and interview was also used. An emetic episode was defined as any episode of vomiting or dry retching.

The patients assessed the intensity of nausea according to a graded scale: none, mild (did not interfere with normal daily life), moderate (interfered with normal daily life) and severe (bedridden due to nausea).

Patient's global satisfaction with antiemetic treatment was assessed using the visual analogue scale (VAS). The patient was asked to place a mark on a 100-mm line where 100 mm was 'not at all satisfied' and 0 mm was 'totally satisfied'.

Each patient reported subjective assessment of general mood day-by-day using a five-point face scale from "QOL assessment of cancer patients receiving chemotherapy" reported by Kurihara and colleagues [30].

We plotted the daily VAS score and daily face scale score on a time curve for each patient. The VAS and face scale profiles were then evaluated on the basis of area under curve (AUC) over the 4-day period calculated by trapezoidal summation, and the difference between the baseline score and worst score during the study period.

2.4. Assessment of safety

All adverse events were documented throughout the study period. Vital signs were recorded before and after the administration of the antiemetic or cytostatic therapy. Routine haematological and biochemical tests were performed at the same times. The severity of each adverse event and its relationship to the study treatment was assessed by the investigator.

2.5. Statistical analysis

The sample size was calculated assuming that 40% of patients assigned to arm A, and at least 65% of the patients of arm B would achieve total control of emesis. With type 1 and 2 errors of 5 and 20%, respectively, it was calculated that 61 patients should be included in each arm. To ensure there would be at least 61 patients assessable for analysis, we decided to include 70 patients in each arm.

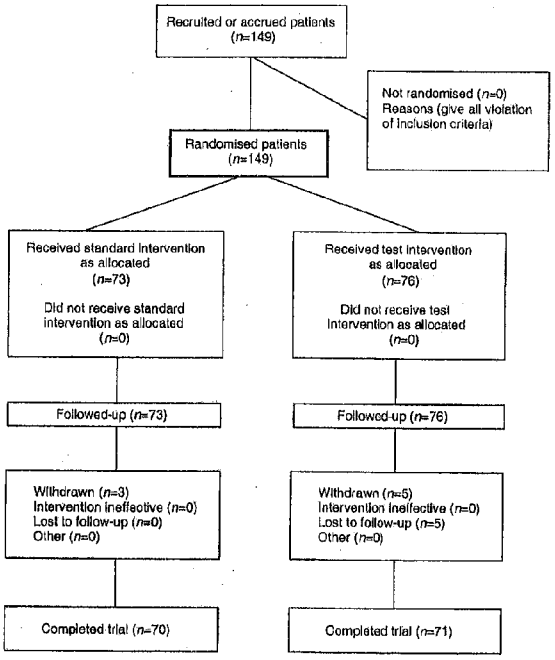

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [29]).

Analysis of nausea and emesis was performed separately for day 1 (acute emesis) and for each day, from day 2 to day 4, considering the overall results between days 2 and 4 as an evaluation of delayed emesis.

Fisher's Exact test was used to evaluate the balance of prognostic factors between the two groups, and to examine differences in efficacy and the incidence of adverse events. Mann–Whitney's U-test was performed to compare treatment groups with respect to intensity of nausea, global satisfaction with antiemetic treatments, and number of emetic episodes. All P values refer to two-tailed tests, and P values less than 0.05 were considered significant.

3. Results

3.1. Patients' characteristics

A total of 149 patients entered the study, and 141 patients were evaluated for efficacy according to the intention-to-treat principle. 8 were lost to follow-up and excluded from the analysis (Fig. 1). Toxicity was also evaluated in these 141 patients. Of the assessable and eligible patients, 70 received dexamethasone alone (arm A) and 71 received ondansetron plus dexamethasone (arm B) as a maintenance treatment. Treatment groups were well balanced for sex, age, daily alcohol consumption, performance status and for cisplatin dose (Table 1).

3.2. Control of acute emesis (day 1)

Overall, complete control of emesis was observed in 93% and control of nausea was observed in 82% of patients. Between the two randomised groups, no significant differences were observed in the complete control of vomiting (arm A versus arm B; 93% versus 93%), of nausea (84% versus 80%), or of both nausea and vomiting (84% versus 79%). Mean number of emetic episodes (0.1 versus 0.1), mean score of maximum intensity of nausea (0.2 versus 0.3), and the number of

Table 1
Patients' characteristics

	Dexamethasone alone	Ondansetron plus dexamethasone	P value
Number of patients	70	71	
Sex: male/female	55/15	58/13	NS
Median age (years) (range)	65 (40–74)	63 (20–72)	NS
Habitual alcohol intake[a]			
No/Yes	28/37	21/46	NS
Performance status (ECOG)			
0–1/2–3	63/7	66/5	NS
Cisplatin dose (mg/m^2)			
<80	13	14	
$\geqslant 80$	57	57	NS
Histological type			
SCLC/NSCLC	16/54	25/46	NS
Clinical stage			
I-III/IV	44/26	42/29	NS

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ECOG, Eastern Co-operative Oncology Group; NS, non significant.
[a], there are missing data in some categories.

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