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Clinical report

A multicenter, double-blind comparison of i.v. and oral administration of ondansetron plus dexamethasone for acute cisplatin-induced emesis

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A total of 530 patients were treated in this multicenter, double-blind, double-dummy, parallel group study to compare the anti-emetic efficacy and safety of a once daily ondansetron oral regimen with a once daily i.v. dosing regimen over a 24 h period, administered to patients prior to receiving cisplatin (50 mg/m^2 or greater) chemotherapy. Patients were randomized to receive a single dose of ondansetron plus dexamethasone given either orally (ondansetron 24 mg and dexamethasone 12 mg, n=262) or i.v. (ondansetron 8 mg and dexamethasone 20 mg, n=268). Complete control of emesis (i.e. no emetic episodes, no rescue and no premature withdrawal) was achieved for 85% of patients (224 of 262) in the oral group and 83% (223 of 268) in the i.v. group. No nausea was reported in 70% of patients in the oral group and 68% in the i.v. group. There were no statistically significant differences between the two groups for any of the assessments of efficacy, which included time to first emetic episode, number of emetic episodes and the worst grade of nausea occurring over the 24 h study period. Once daily ondansetron oral and i.v., in combination with dexamethasone, was well tolerated in this study. In conclusion, once daily oral ondansetron 24 mg plus dexamethasone is equally effective in the control of emesis and nausea induced by highly emetogenic chemotherapy as once daily ondansetron 8 mg i.v. plus dexamethasone. [**]**

Key words: Acute phase, cisplatin, emesis, nausea, ondansetron, oral.

Introduction

Ondansetron, the first selective 5-HT$_3$ receptor antagonist to be licensed, is well-tolerated and highly effective in the control of emesis (retching and vomiting) and nausea in patients receiving cytotoxic chemotherapy and radiotherapy. Single dose i.v. ondansetron 8 mg and dexamethasone 20 mg i.v. is an effective regimen for the prevention of acute emesis and nausea (the first 24 h) after highly emetogenic chemotherapy such as cisplatin.

Both i.v. and oral ondansetron have been studied in cancer patients receiving chemotherapy, with ondansetron i.v. being effective in this indication over the dose range 8–32 mg.[1,2] Ondansetron is superior to conventional anti-emetics such as high-dose metoclopramide[3] and the efficacy is enhanced when combined with a corticosteroid such as dexamethasone.[4] Ondansetron plus dexamethasone is superior to the combination of metoclopramide, dexamethasone and diphenhydramine,[5] and to the combination of metoclopramide, dexamethasone and lorazepam in the control of acute cisplatin-induced emesis and nausea.[6]

Chemotherapy regimens for various malignancies are often given as outpatient treatments and a simple once daily oral dosing regimen would offer a useful alternative to once daily i.v. dosing. This study (protocol S3AB3008) was designed to compare the efficacy and safety of once daily oral ondansetron with an established i.v. regimen in the prevention of acute emesis and nausea following highly emetogenic chemotherapy (50 mg/m^2 or greater cisplatin). This was achieved by comparing the safety and efficacy of the once daily oral dosing regimen of ondansetron 24 mg in combination with dexamethasone 12 mg with once daily ondansetron 8 mg i.v. and dexamethasone 20 mg i.v.

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Materials and methods

Conduct of the study

This was a multicenter, randomized, double-blind, double-dummy, parallel group study carried out at 30 centers in eight countries (Canada, France, Germany, Iceland, Italy, Poland, South Africa and the UK). The study was conducted in accordance with Good Clinical Practice Guidelines and to the principles of the Declaration of Helsinki as modified by the 41st World Medical Assembly, Hong Kong 1989. The protocol received approval from all Regulatory Authorities and local Ethics Committees as appropriate to the countries in which the study was carried out. Informed consent was obtained from patients prior to entry into the study.

Patients

Male and female cancer patients aged at least 18 years, scheduled to receive their first dose of their first course of cisplatin chemotherapy (with or without other cytotoxics) administered as a single i.v. dose of 50 mg/m^2 or greater over a period of up to 4 h, were included.

Patients were excluded if they had received chemotherapy during the previous 6 months, abdominal or pelvic irradiation in the previous 48 h, anti-emetic therapy during the previous 24 h, or an investigational drug in a clinical trial in the previous 30 days, or were scheduled to receive such a drug or an anti-emetic, or such radiotherapy during the study. Patients were excluded if they had experienced emesis and/or moderate/severe nausea in the previous 24 h, had contraindications to ondansetron or dexamethasone use, moderate or severely impaired hepatic function, severe concurrent illness (other than neoplasia), medical conditions that might confound the evaluation of the data, or other etiologies for emesis and nausea (e.g. gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, active peptic ulcer disease or central nervous system tumors).

Populations and sample size

Safety results shown are from the Safety population which included all patients who were randomized into the study and received active anti-emetic study medication in either the once daily oral or i.v. formulations, but not both. The efficacy results reported were from the Intent-to-Treat population: all patients in the Safety population who received cisplatin-containing chemotherapy.

It was calculated that a study sample size of 504 (equally divided between the two treatment groups) would have 80% power to detect a 12% or greater difference between the groups in the proportion of patients with complete control of emesis (no emetic episodes in 24 h), on the assumption that i.v. treatment would provide complete control in a minimum of 70% of patients.

Treatment

Patients were allocated to the once daily oral or i.v. group according to a pre-determined computer-generated randomization code. Treatments were administered double-blind, using a double-dummy design with oral active treatment (or placebo) being given 1–2 h before cisplatin infusion, and i.v. active treatment (or placebo) being given as two injections 10 and 5 min before cisplatin infusion. The oral treatment group received three 8 mg ondansetron tablets and two 6 mg dexamethasone capsules, followed by i.v. placebo injections (sodium chloride 0.9% w/v); the i.v. treatment group received oral placebo (three tablets and two capsules to match the active treatment) and then dexamethasone 20 mg i.v. followed by ondansetron 8 mg i.v. Chemotherapy with a cisplatin dose of 50 mg/m^2 or greater was administered i.v. over a period of up to 4 h. Ondansetron tablets and injection were provided as the hydrochloride dihydrate salt; dexamethasone as the sodium phosphate salt. Dexamethasone tablets were encapsulated to facilitate placebo-blinding. All drug supplies were accounted for on a study drug accountability log kept by the pharmacist.

Efficacy assessments

Diary cards were completed over a 24 h efficacy assessment period from the start of cisplatin infusion. The times of emetic episodes were recorded. Emesis was defined as a single vomit or retch, or any number of continuous vomits or retches. An emetic episode was, by definition, separated by the absence of vomiting or retching for at least 1 min. Withdrawal and the administration of rescue medication for emesis or nausea was recorded. The occurrence of nausea was recorded as present or absent and, if present, the worst nausea

grade during the 24 h efficacy assessment period was rated as mild, moderate or severe.

Safety assessments

All adverse events were documented during treatment: from the time of ingestion of the oral study treatment to 24 h after the start of cisplatin infusion and post-treatment: from 24 h following the start of the cisplatin infusion to the follow-up visit, conducted between 24 h and 28 days after the start of cisplatin infusion. The severity of each adverse event and the relationship to study treatment was assessed by the investigator. Serious adverse events were defined as those that were fatal, life-threatening, disabling, incapacitating, requiring or prolonging hospitalization, congenital anomaly in offspring, cancer, events resulting from overdosage and laboratory abnormalities of major clinical concern.

Statistical methods

All efficacy data analyses were stratified by country clusters each comprising a minimum of 20 patients (Canada, France, Poland, South Africa and the UK). A sixth cluster consisted of the single centers in Germany, Iceland and Italy.

The primary outcome measure was the proportion of patients with complete emetic control, i.e. with no emesis, no rescue and no withdrawal in the 24 h study period, which was compared between the treatment groups using a Mantel-Haenszel χ^2 test. Secondary measures were (i) the number of emetic episodes, classified as 0, 1, 2, 3 and >3, with rescued or withdrawn patients assigned a score of >3, and compared between groups using a Wilcoxon rank sum test; (ii) the time to the first emetic episode or to withdrawal or rescue, and compared between treatment groups using a logrank test; and (iii) nausea severity compared between groups using a Wilcoxon rank sum test, with withdrawn and rescued patients scored as severe. Logistic regression modeling of complete emetic control rates was used to assess the effects of prognostic factors (age, sex, Caucasian or non-Caucasian race, weight, height, body surface area, cisplatin chemotherapy dose and alcohol use or non-use) and their interaction with treatment.

Safety analyses were conducted for the period during treatment and for the post-treatment period separately, comparing the incidence of the most common adverse events (occurring in 5% or more of patients in at least one of the two treatment groups) using Fisher's Exact test.

Results

Patient characteristics

Of the 543 patients recruited, one was not randomized to treatment, four did not receive active study medication, and eight received both oral and i.v. active treatments. The Safety and the Intent-to-Treat populations therefore comprised 530 patients, 262 in the oral treatment group and 268 in the i.v. treatment group. Of these patients, 27 (10%) in the oral group and 30 (11%) in the i.v. group had at least one major protocol violation: the largest single category of violation was the taking of excluded antiemetic medication during treatment, other than as rescue medication: 16 (6%) in the oral group and 12 (4%) in the i.v. group.

The two treatment groups were well balanced with respect to demographic factors (Table 1). The

Table 1. Patient demography for Intent-to-Treat population

	Treatment group	
	Oral	i.v.
Number of patients	262	268
Sex		
male	159 (61%)	164 (61%)
female	103 (39%)	104 (39%)
Age (years)		
mean (±SD)	53 (±13)	53 (±14)
range	19–81	19–86
Ethnic origin		
caucasian	225 (86%)	232 (87%)
black	23 (9%)	23 (9%)
other	14 (5%)	13 (5%)
Weight (kg)		
mean (±SD)	67.6 (±13.8)	68.7 (±14.3)
range	37.0–112.0	35.0–115.0
Weekly alchohol use (units[a])		
0	178 (69%)	185 (71%)
1–20	59 (23%)	62 (24%)
>20	21 (8%)	12 (5%)
not recorded	4	9
Type of tumor[b]		
lung	66 (25%)	72 (27%)
gynecological	64 (24%)	64 (24%)
head and neck	48 (18%)	48 (18%)
genitourinary	38 (15%)	32 (12%)
gastrointestinal	18 (7%)	30 (11%)
other	30 (11%)	26 (10%)

[a]Unit of alcohol=one measure of spirit, one glass of wine or 250 ml of beer.
[b]Patients can have more than one primary tumor site.

most common primary tumor site was the lung (26%). Chemotherapy regimens were very similar in the two groups with respect to cisplatin dose and additional cytotoxic agents (Table 2).

Table 2. Most common[a] chemotherapy regimens for Intent-to-Treat population

	Treatment group	
	Oral	i.v.
Number of patients	262	268
Cisplatin with fluorouracil	52 (20%)	65 (24%)
Cisplatin with etoposide	53 (20%)	55 (21%)
Cisplatin with cyclophosphamide	50 (19%)	49 (18%)
Cisplatin dose (mg/m^2)		
median	75	75
<70	103 (39%)	103 (38%)
⩾70	159 (61%)	165 (62%)
⩾100	70 (27%)	63 (24%)

[a]Most common defined as more than 10% of patients receiving the cytotoxic agent. Between 5 and 10% of patients received vinblastine, bleomycin, mitomycin, epirubicin, vinorelbine tartrate or doxorubicin hydrochloride with cisplatin.

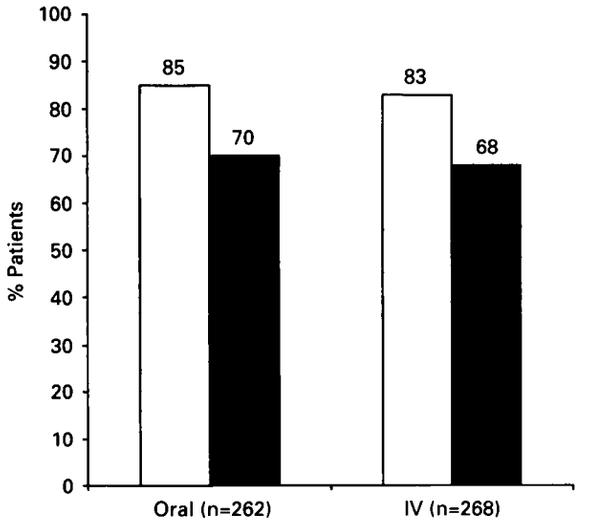

Figure 1. Control of emesis and nausea after oral or i.v. treatment. Open bars, complete emetic response (no emetic episodes, no rescue or premature withdrawal); solid bars, no nausea. Percentage of patients with complete control of emesis and nausea over the 24 h efficacy assessment period. There were no statistically significant differences in the incidences of either parameter between the oral ondansetron 24 mg plus dexamethasone 12 mg group and the i.v. ondansetron 8 mg plus dexamethasone 20 mg group.

Control of emesis and nausea

Complete control of emesis (i.e. no emetic episodes, rescue or withdrawal) over 24 h was achieved in 85% of oral and 83% of i.v. treated patients (Figure 1). The difference between the rates was 2.3% [95% confidence interval (CI): −3.9, 8.5%] which was not statistically significant (p=0.05). Furthermore, at cisplatin doses of 100 mg/m^2 or above, the complete emetic control rates were similar between the oral and i.v. treatment groups: 79 and 81%, respectively.

No nausea was reported for 70% of oral and 68% of i.v. treated patients (Figure 1 and Table 3). Table 3 shows the distribution of numbers of patients with different grades of nausea severity which did not differ significantly between the two groups (p=0.65).

Table 4 shows the distribution of numbers of patients with different numbers of emetic episodes; the distribution did not differ significantly between the two groups (p=0.57). The log-rank test showed

Table 3. Severity of nausea in the Intent-to-Treat population

	Treatment group	
	Oral	i.v.
Number of patients	262	268
Nausea grade		
None	184 (70%)	183 (68%)
Mild	40 (15%)	49 (18%)
Moderate	17 (6%)	11 (4%)
Severe	2 (<1%)	10 (4%)
Rescued or withdrawn	19 (7%)	15 (6%)

Table 4. Number of emetic episodes in the Intent-to-Treat population

	Treatment group	
	Oral	i.v.
Number of patients	262	268
Number of emetic episodes		
0	224 (85%)	223 (83%)
1	8 (3%)	16 (6%)
2	6 (2%)	4 (1%)
3	1 (<1%)	9 (3%)
>3 (not rescued)	4 (2%)	1 (<1%)
0–3 (rescued)	9 (3%)	8 (3%)
>3 (rescued)	8 (3%)	7 (3%)
withdrawn (not rescued)	2 (<1%)	0 (0%)

the survival curves of time to first emetic episode or treatment failure from the start of cisplatin therapy did not significantly differ between the two groups (p=0.56). For patients with any emetic episode or failure, the median times to first occurrence were 17 and 15 h in the oral and i.v. groups, respectively.

Logistic regression analysis of complete emetic control showed better control in males compared to females ($p<0.001$), with lower cisplatin dose ($p<0.001$), with greater age (p=0.021), for non-Caucasians compared to Caucasians (p=0.045) and with increased alcohol intake (p=0.056). After adjustment for these factors and for country clusters, the odds ratio for complete control with oral treatment compared to i.v. treatment was 1.22 (95% CI: 0.73, 2.03; p=0.46).

Tolerability

Ondansetron in combination with dexamethasone was well tolerated in both the once daily oral and i.v. treatment groups with no statistically significant differences between the groups, either in the overall rate of adverse events during treatment (21 and 22% in the respective groups) or in the rates of occurrence of the most common adverse effects: constipation occurred in 6% of patients in the oral group and 4% in the i.v. group, and headaches in 8% of both groups (Table 5). Constipation and headache are well recognized side effects of 5-HT_3 receptor antagonists. The incidences of both adverse events were low after treatment.

Serious adverse events were rare, occurring in four (1.5%) patients in each group during the entire study. Three patients (one in the oral and two in the i.v. group) had serious adverse events during treatment. None were assessed as likely to be due to the study treatment. Two patients (below 1%) from the oral group withdrew from the study due to adverse events during treatment. Both patients withdrew due to nausea and emesis.

Table 5. Incidence of the most common[a] adverse events in the Safety population

Treatment group	During treatment		Post treatment	
	Oral	i.v.	Oral	i.v.
Number of patients	262	268	262	268
Any adverse event	55 (21%)	59 (22%)	19 (7%)	18 (7%)
Constipation	16 (6%)	10 (4%)	3 (1%)	4 (1%)
Headaches	22 (8%)	21 (8%)	1 (<1%)	1 (<1%)

[a]Most common defined as 5% or more patients in at least one group; some patients experienced more than one adverse event.

Discussion

The incidence of acute emesis and nausea (in the first 24 h after chemotherapy) is greater than 90% in patients receiving highly emetogenic chemotherapy, such as cisplatin, dacarbazine and mechlorethamine, unless treated with anti-emetic agents.[7] Good control of these symptoms following chemotherapy is an important prognostic factor for later control of delayed emesis and nausea (symptoms occurring more than 24 h after the start of chemotherapy), and of emesis and nausea experienced in subsequent chemotherapy cycles.[4,8] It is therefore important that emesis and nausea should be well controlled on the first cycle of chemotherapy, as this may have a significant effect on the patient's quality of life and willingness to complete their course of treatment.[9,10] Furthermore, uncontrolled emesis frequently results in poor nutritional status and dehydration.[11]

This study showed that a once daily oral dose of ondansetron 24 mg plus dexamethasone 12 mg was as effective as the i.v. dosing regimen (once daily ondansetron 8 mg and dexamethasone 20 mg) for highly emetogenic chemotherapy. In this study, the highly emetogenic chemotherapy challenge was provided by the administration of cisplatin (50 mg/m^2 or greater). The median dose of cisplatin administered was 75 mg/m^2, with approximately 25% of patients receiving more than 100 mg/m^2.

Over the 24 h efficacy assessment period, complete control of emesis (with no emetic episodes, rescue or withdrawal) was achieved in 85% of patients receiving once daily oral medication and 83% receiving once daily i.v. medication, with no statistically significant difference between the groups. Similar efficacy rates were seen between the groups in patients receiving cisplatin doses of 100 mg/m^2 or greater. Absence of nausea was experienced by similar percentages of patients in the two groups: 70% with oral treatment and 68% with i.v. treatment. Other assessments of efficacy, such as time to first emetic episode, number of emetic episodes and worst grade of nausea over the 24 h study period showed no statistically significant difference between the oral and i.v. groups.

Ondansetron administered once a day orally or i.v. in combination with dexamethasone was well toler-

ated. The most common adverse events during treatment were headaches and constipation, occurring at similar rates in the two groups. These are already well recognized effects of ondansetron.

Conclusion

A once daily oral dose of ondansetron 24 mg plus dexamethasone 12 mg orally is as effective as the once daily i.v. dosing schedule, and will offer a useful alternative to i.v. dosing for acute emesis and nausea after highly emetogenic chemotherapy, especially when the requirement is for effective and well-tolerated anti-emetic treatment which is simple and convenient to administer.

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