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Original Paper

A Double-blind, Randomised Comparison of the Anti-emetic Efficacy of Two Intravenous Doses of Dolasetron Mesilate and Granisetron in Patients Receiving High Dose Cisplatin Chemotherapy

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This multicentre, double-blind, double-dummy, randomised trial was designed to compare the efficacy and safety of single intravenous doses of dolasetron mesilate and granisetron in the prevention of acute emesis and nausea due to high-dose (≥80 mg/m²) cisplatin. Single intravenous doses of 1.8 or 2.4 mg/kg of dolasetron mesilate or 3 mg of granisetron hydrochloride were administered in a volume of 50 ml over a 5-min period, beginning 30 min prior to cisplatin (≥80 mg/m²) administration. The number and timing of emetic episodes, time to administration of escape anti-emetic medication, severity of nausea by visual analogue scale (VAS), and safety were monitored for 24 h after the start of cisplatin-containing chemotherapy. Investigators' evaluations of overall efficacy and patients' satisfaction with therapy were recorded at the end of the 24-h study period. Of the 474 patients evaluable for efficacy, complete responses were achieved by 54, 47 and 48% of patients given dolasetron mesilate 1.8 mg/kg, dolasetron mesilate 2.4 mg/kg and granisetron, respectively. Statistically, treatment groups had comparable complete and complete plus major responses, times to first emesis, and use of escape medication; patient maximum nausea severity and treatment satisfaction ratings; and physician nausea severity and overall efficacy assessments. For the majority of efficacy endpoints, 1.8 mg/kg dolasetron mesilate produced numerically superior responses compared with the 2.4 mg/kg dose. Gender and prior chemotherapy were significant predictors of complete response; males and chemotherapy-naive patients had higher responses. The overall incidences of adverse events were comparable among the treatment groups; headache and diarrhoea were most common. In conclusion, 1.8 and 2.4 mg/kg of dolasetron mesilate and granisetron (3 mg) were equally effective in preventing nausea and vomiting induced by highly emetogenic cisplatin-containing chemotherapy. In addition, because no additional benefit was observed with 2.4 mg/kg of dolasetron mesilate and numerically greater responses were observed with the 1.8 mg/kg dose, the lower dose of 1.8 mg/kg is optimal for further clinical development.

Key words: anti-emetic, cisplatin, clinical trial, dolasetron, emesis, granisetron, nausea, serotonin, 5-HT$_3$ receptor antagonist

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INTRODUCTION

CHEMOTHERAPY-INDUCED nausea and vomiting are a primary concern in the treatment of patients with malignant disease [1]. Failure to control nausea and emesis can lead to serious medical complications, poor quality of life and a potentially life-threatening failure to continue with treatment [2]. The new highly selective and potent serotonin receptor (5-HT_3) antagonists have led to a major improvement in the prevention and control of nausea and vomiting after cytotoxic chemotherapy [3,4]. The 5-HT_3 antagonists have been shown to be as effective as or more effective than traditional metoclopramide regimens [5–8] without the risk of extrapyramidal side-effects associated with metoclopramide [3,9,10]. In addition, some of these new agents offer the convenience of once-daily dosing and the administration of single intravenous (i.v.) doses [4].

Dolasetron mesilate (Anzemet®, Hoechst Marion Roussel, Inc.) is a new pseudopelletierine-derivative with properties typical of other 5-HT_3 antagonists. It is a potent antagonist of 5-HT_3 receptors, is highly selective [11–13], and is rapidly and almost completely metabolised to a more potent and more selective metabolite, MDL 74,156, that possesses a longer half-life [14]. Development of the drug dosing was based on the mesilate salt. Hence, all references to dose refer to the salt which can be adjusted to the equivalent base by multiplying by 0.74. The results of open-label, dose-ranging studies have suggested that dolasetron has substantial anti-emetic effects and a large therapeutic index in patients receiving moderately or highly emetogenic chemotherapy [15–19]. These studies also demonstrated that the minimum efficacious dosage was a single i.v. dose of 1.8 mg/kg and that efficacy did not increase substantially at higher single i.v. doses.

The results of dolasetron dose-ranging studies have been confirmed in double-blind, randomised trials in patients undergoing high-dose cisplatin-containing chemotherapy [20, 21]. Patients who received a single 1.8 mg/kg dose of dolasetron mesilate had significantly higher complete responses (no emetic episodes and no need for escape anti-emetic medication), complete plus major responses ($\leq$2 emetic episodes and no need for escape anti-emetic medication), and significantly longer times to the first emetic episode compared with those who received 0.6 mg/kg [21]. Further, Harman and associates [20] demonstrated that a single i.v. 1.8 mg/kg dose of dolasetron mesilate was significantly more effective than a multiple dose regimen (0.6 mg/kg × 3).

Our study was the first large, multicentre trial designed to compare two different i.v. doses of dolasetron mesilate with granisetron in a three-arm, double-blind, double-dummy manner whose objectives were 3-fold. The first was to determine if i.v. dolasetron mesilate given as a single dose of 1.8 or 2.4 mg/kg was as effective as or more effective than i.v. granisetron administered as a single 3-mg dose in preventing emesis due to high-dose cisplatin chemotherapy. The second was to compare the tolerability of dolasetron and granisetron and the third was to compare patient satisfaction for each of the three anti-emetic regimens. Granisetron was used in the comparator arm of the study because numerous studies have shown that single i.v. doses were safe and effective in controlling chemotherapy-induced nausea and emesis in patients receiving cisplatin chemotherapy [22–25]. In addition, this is the first large, multicentre trial to stratify prospectively patients according to gender and prior history of chemotherapy before randomisation to treatment.

PATIENTS AND METHODS

Patients

Male or female patients over the age of 18 years who had histologically confirmed malignant disease and a Karnofsky performance status of $\geq$50% were eligible for the study. All patients were scheduled to receive cisplatin as the first component of a chemotherapy regimen at a dose of $\geq$80 mg/m^2 over no more than 3 h. Both chemotherapy-naive patients and patients who had previously undergone cytotoxic chemotherapy were admitted into the study. The results of laboratory determinations were required to be within the normal ranges or attributable to the patients' primary disease. The protocol for this study was approved by the appropriate Institutional Review Boards, and all patients gave written informed consent.

Patients who had a history of significant neurological or psychiatric illness (except alcoholism), a history of congestive heart failure, arrhythmias requiring medication, heart block greater than first degree, cardiotoxicity due to cumulative doses of anthracyclines or anthracenediones, abnormal serum potassium or calcium concentrations, or evidence of clinically significant liver disease were excluded from the study. Also excluded were patients who had received investigational drugs within 21 days of the trial, chemotherapy in the 72 h prior to cisplatin, and treatments that could interfere with interpretation of the study results. Patients who, within the 24 h preceding chemotherapy, had experienced vomiting or nausea with a severity of 2–4 according to the Southwest Oncology Group scale were also disqualified, as were patients who had experienced vomiting from any organic aetiology. Pregnant women and women with uninhibited childbearing potential and patients with body weight >83 kg (because of problems in using the double-dummy infusion) were also prohibited from entering the study.

Study procedures

Patients underwent pretreatment screening between 3 and 7 days before the start of cisplatin therapy. Eligible patients were then stratified by gender (male, female) and previous chemotherapy status (naive, non-naive) and randomly assigned within each centre and each strata to receive single i.v. doses of 1.8 mg/kg of dolasetron mesilate, 2.4 mg/kg of dolasetron mesilate, or 3 mg of granisetron.

Thirty minutes prior to the administration of cisplatin, patients received an infusion of the assigned study drug over a period of 5 min. Granisetron hydrochloride was supplied in 3 ml ampoules (1 mg/ml) and dolasetron mesilate in 10 ml ampules (20 mg/ml); matching placebo ampoules were prepared for each treatment. Dosing of dolasetron was based on the patient's body weight while granisetron was given as a fixed dose of 3 mg. So that the trial remained blind, the required volume of dolasetron (or placebo) was added to 3 ml of placebo (or granisetron) and the final volume was made up with sterile NaCl 0.9% so that each patient received a total infusion of 50 ml. Cisplatin was administered i.v. as the first component of the chemotherapy regimen at a dose of $\geq$80 mg/m^2 over no more than 3 h. Within each centre, cisplatin infusion was administered at the same time period during the day; the beginning of cisplatin therapy was designated as hour 0.

Patients remained in the hospital for at least 8 h after the start of chemotherapy (except at one centre where they were released after 6 h) and were monitored during the 24 h follow-

ing the initiation of chemotherapy; most patients were hospitalised for the entire 24-h study period. Patients who did not remain hospitalised for the 24-h study period were required to return to the hospital 24 h after the start of chemotherapy for final study evaluations. Patients who suffered three or more emetic episodes during the first 24 h could receive escape anti-emetic medication, as did any patient who requested additional anti-emetic medication at any time during the study.

Evaluation of efficacy

Efficacy was evaluated throughout the 24 h following the start of cisplatin chemotherapy by recording the number of emetic episodes experienced by each patient. An emetic episode was defined as one occurrence of vomiting or a sequence of occurrences in very close succession not relieved by a period of relaxation, any number of occurrences of unproductive emesis (retches) in a unique 5-min period, or an episode of retching of less than 5 min duration combined with vomiting not relieved by a period of relaxation. Anti-emetic efficacy was evaluated as follows: a complete response was defined as no emetic episodes and no use of escape anti-emetic medication and, a major response was defined as one or two emetic episodes and no use of escape anti-emetic medication in the 24 h after the start of chemotherapy. A treatment failure was defined as any patient who either had three or more emetic episodes or received escape anti-emetic medication during the 24 h after initiation of chemotherapy. Any patient who was not evaluated for emesis for at least 23.5 h after the start of chemotherapy was also categorised as a treatment failure. In addition, the time to the first emetic episode and the time to escape medication were recorded.

Patients rated the severity of nausea 45 min before, immediately before and 24 h after the start of cisplatin infusion (hour 0) according to a visual analogue scale (VAS) that ranged from "no nausea" (0 mm) to "nausea as bad as it can be" (100 mm). At hour 24, patients rated their most severe episode of nausea during the previous 24 h. The nausea assessments 45 min before and immediately before cisplatin rated the patient's nausea at that particular time. Patient satisfaction with their anti-emetic regimen was also evaluated according to a VAS of "not at all satisfied" (0 mm) to "completely satisfied" (100 mm). In addition, a global assessment of efficacy was made by investigators according to a rating scale of 0 to 3 (no, slight, good, excellent efficacy), while the patient's most severe nausea during the 24-h evaluation period was rated by investigators according to a discrete scale of 0 to 3 (no, slight, moderate, severe nausea).

Evaluation of safety

Patients underwent physical examinations and clinical laboratory tests prior to treatment and again at the 24-h visit. Vital signs were assessed 15 min prior to study medication and at 0.5, 4, 8 and 24 h after the start of cisplatin. Electrocardiograms (ECGs) were obtained within 3 days prior to treatment for all patients and 1–2 and 24 h after cisplatin for patients at some centres. All patients were monitored for adverse events throughout the 24-h treatment period.

Statistical analyses

A sample size of 100 patients per treatment group was estimated as described previously [26], based on $\alpha = 0.10$, $\beta = 0.20$, and an assumed complete response rate of 70% per treatment. 150 patients per treatment group were deemed necessary in order to compensate for potential withdrawals and to allow for addition estimation precision. A difference of 15% in the response rates between treatment groups was necessary to conclude superiority; otherwise, treatments were concluded to be equivalent. This was true for complete response rates in the overall population and not for analyses of response rates within and between strata.

The primary efficacy endpoint was complete response. The secondary efficacy endpoints were complete plus major response, time to first emetic episode or use of escape anti-emetic medication, patients' VAS ratings of maximum severity of nausea over the 24-h period, patients' VAS ratings of overall satisfaction with anti-emetic treatment, investigators' ratings of maximum nausea severity and investigators' global evaluation of efficacy. All analyses were performed with the intent-to-treat data set, which included data from all patients randomly assigned to treatment who received the study medication. Baseline patient characteristics were compared among the treatment groups by the Kruskal–Wallis one-way analysis of variance for quantitative variables and the chi-square or Fisher's Exact test for categorical variables. The treatment groups were compared with respect to the percentage of patients with a complete response by logistic regression with confidence intervals for the odds ratio controlling for stratum (male, female, chemotherapy-naive, prior chemotherapy). Logistic regression and a main effect test was used to test for differences in response rates across levels of each factor (such as across strata). Pairwise confidence intervals and hypothesis tests were used to test differences between the treatment groups. All tests were two-sided with $\alpha = 0.05$. Complete or major response rates were also compared among treatment groups with the logistic regression method used for complete response.

Time to first emetic episode or use of escape anti-emetic medication was analysed by survival techniques (SAS PHREG procedure). A rank analysis of variance was used to compare the treatment groups with respect to patient VAS ratings of maximum severity of nausea and satisfaction with anti-emetic treatment. A Mantel–Haenszel row mean scores difference test was used to compare the groups with respect to the investigators' rating of maximum severity of nausea and global assessment of efficacy.

RESULTS

Patients

A total of 476 patients were enrolled into the study at 29 investigative centres. Of these, 474 were included in the intent-to-treat dataset: 163 in the dolasetron mesilate 1.8 mg/kg group, 161 in the dolasetron mesilate 2.4 mg/kg group, and 150 in the granisetron group. 2 patients assigned to treatment did not receive study medication and were excluded from the analysis.

The three treatment groups were comparable at baseline with respect to demographic characteristics (Table 1), previous exposure to chemotherapy, Karnofsky performance status, history of alcohol abuse and severity of nausea at hour 0. The distribution of the sites of primary neoplasm was also comparable across the treatment groups; the most frequent sites were head and neck (36%), lung (15%), digestive system (14%) and female reproductive organs (14%). The groups were balanced with respect to the duration of cisplatin infusion, the interval between the administration of study drug

Table 1. Demographic and baseline characteristics of patients treated with single i.v. doses of 1.8 or 2.4 mg/kg of dolasetron mesilate or 3 mg of granisetron

Variable	Dolasetron mesilate 1.8 mg/kg ($n = 163$)	Dolasetron mesilate 2.4 mg/kg ($n = 161$)	Granisetron 3 mg ($n = 150$)
Gender [*n* (%)]			
Male	105 (64)	110 (68)	100 (67)
Female	58 (36)	51 (32)	50 (33)
Age (years)			
Mean ± S.D.	54 ± 11	54 ± 13	56 ± 12
Previous chemotherapy [*n* (%)]			
Naive	96 (59)	99 (61)	90 (60)
Non-naive	67 (41)	62 (39)	60 (40)
Stratification [*n* (%)]			
Male naive	68 (42)	77 (48)	67 (45)
Female naive	28 (17)	22 (14)	23 (15)
Male non-naive	37 (23)	33 (20)	33 (22)
Female non-naive	30 (18)	29 (18)	27 (18)
Karnofsky status (%)			
Mean ± S.D.	85 ± 11	86 ± 11	85 ± 11
Cisplatin dose (mg/m^2)*			
Mean ± S.D.	96 ± 12	96 ± 11	98 ± 11

*Significantly different at $P < 0.05$.
S.D., standard deviation.

and cisplatin, and the percentage of patients who received concomitant chemotherapy. Although the dose of cisplatin administered was significantly different ($P = 0.0389$) across the treatment groups, the magnitude of the difference (2 mg/m^2) was not considered to be clinically significant (Table 1).

Efficacy evaluations

All three treatment regimens were effective in controlling cisplatin-induced emesis. While the responses to both doses of dolasetron mesilate were comparable to that of granisetron, 1.8 mg/kg of dolasetron mesilate produced numerically greater responses for most efficacy endpoints compared with 2.4 mg/kg. There were no significant differences between the three treatment groups with respect to the percentages of patients with complete responses or complete plus major responses (Table 2). Complete responses were achieved by 54, 47 and 48% of patients receiving 1.8 mg/kg dolasetron mesilate, 2.4 mg/kg dolasetron mesilate and 3 mg granisetron, respectively. Complete plus major response rates ranged from 62 to 63% for the three treatment groups. The median times to first emetic episode or use of escape medication were >24.00 h in the dolasetron mesilate 1.8 mg/kg group, 22.21 h in the dolasetron mesilate 2.4 mg/kg group and 23.17 h in the granisetron group. There were no significant between-group differences, although 1.8 mg/kg of dolasetron mesilate was numerically superior to the 2.4 mg/kg dose.

The complete response rates within the patient strata showed trends that were consistent with those for the population as a whole; dolasetron and granisetron were comparable, but 1.8 mg/kg of dolasetron mesilate appeared to be numerically superior to the 2.4 mg/kg dose. Statistical significance was not reached between the treatment groups primarily due to the small sample sizes for each of the subgroups. However, response rates differed significantly across the various strata ($P = 0.0001$) (Table 2). Males responded better than females ($P = 0.0001$), and naive patients better than non-naive patients ($P = 0.0008$). Subgroup analyses revealed no differences in the effect of treatment across the specifically defined subgroups of age (<65 years or ≥65 years), cisplatin dose (≤90 mg/m^2 or >90 mg/m^2), Karnofsky status (<80% or ≥80%), or history of alcohol abuse. However, history of alcohol abuse was associated with a significantly higher ($P = 0.0317$) overall level of complete response.

The treatment groups were comparable with respect to the patients' VAS ratings of the maximum severity of nausea over the 24-h period and the investigators' assessments of the maximum severity of patients' nausea over 24 h (Table 3). There was, however, a trend toward better nausea control with the 1.8 mg/kg dose of dolasetron compared with the 2.4 mg/kg dose. Forty-one per cent of the patients in each treatment group reported no nausea (VAS score of ≤5 mm). The percentages of patients categorised by the investigator as having no nausea were consistent with results of the patients' VAS ratings. Patients' VAS ratings of their satisfaction with anti-emetic therapy were similar across the three treatment groups, as were the mean scores for the investigator's global assessment of anti-emetic efficacy. The investigator rated anti-emetic efficacy as good or excellent in 61% of patients in the dolasetron mesilate 1.8 mg/kg group, 62% of patients in the dolasetron mesilate 2.4 mg/kg group and 62% of patients in the granisetron group.

Safety

There were no statistically significant differences in the overall incidence of adverse events between the dolasetron mesilate 1.8 mg/kg (58%, 94/163), dolasetron mesilate 2.4-mg/kg (55%, 88/161), and granisetron (45%, 67/150) treatment groups. Similarly, there were no statistically significant differences between the treatment groups for individual adverse events (Table 4). The most frequently reported adverse events in all three treatment groups were headache and diarrhoea and were primarily mild to moderate in intensity. Severe adverse events were noted in 6, 7 and 5% of patients who received 1.8 mg/kg dolasetron mesilate, 2.4 mg/kg dolasetron mesilate and granisetron, respectively. There was no significant effect of treatment on the incidence of severe adverse events. All the severe events were considered unrelated to the study medication except for angina/myocardial infarction/acute pulmonary oedema and fever/adominal pain in 2 patients in the granisetron group. These events were considered possibly related to study medication.

ECGs were available for 442 patients at baseline, 249 patients at hour 1–2 and 301 patients at hour 24. Treatment-emergent ECG effects, as evidenced by increases in the QT_c and PR intervals and QRS duration, occurred with all three study medications but were deemed to be clinically non-significant by the investigators. For the QT_c interval, the magnitude of the increases was small at 24 h and there were no significant differences between the three treatment groups. At 1–2 hours post-treatment, patients who received dolasetron had significantly greater ($P = 0.0016$) increases in QT_c interval compared to those given granisetron. The mean changes in PR interval at 1–2 hours post-treatment were also significantly higher ($P = 0.0002$) for dolasetron patients compared with patients who received granisetron. No significant differences between the treatment groups were observed at 24 h post-

Table 2. Response to anti-emetic treatment with single i.v. doses of 1.8 or 2.4 mg/kg of dolasetron mesilate or 3 mg of granisetron

Response and patients analysed	Dolasetron mesilate 1.8 mg/kg	Dolasetron mesilate 2.4 mg/kg	Granisetron 3 mg
Complete response*			
Population as a whole	88/163 (54%)	75/161 (47%)	72/150 (48%)
Population strata			
Male naive	48/68 (71%)	44/7 (57%)	42/67 (63%)
Female naive	12/28 (43%)	6/22 (27%)	4/23 (17%)
Male non-naive	22/37 (59%)	19/33 (58%)	18/33 (55%)
Female non-naive	6/30 (20%)	6/29 (21%)	8/27 (30%)
Male	70/105 (67%)	63/110 (57%)	60/100 (60%)
Female	18/58 (31%)	12/51 (24%)	12/50 (24%)
Naive	60/96 (63%)	50/99 (51%)	46/90 (51%)
Non-naive	28/67 (42%)	25/62 (40%)	26/60 (43%)
Complete plus major response†	101/163 (62%)	100/161 (62%)	95/150 (63%)

*Complete response defined as no emetic episodes and no use of escape medication. †Complete plus major response defined as ≤2 emetic episodes and no use of escape medication.

Table 3. Assessment of most severe nausea over 24 h evaluation period

Score analysed	Dolasetron mesilate 1.8 mg/kg	Dolasetron mesilate 2.4 mg/kg	Granisetron 3 mg
Patients' VAS score*			
n	158	158	148
Mean ± S.E.M.	34 ± 3.0	38 ± 3.1	36 ± 3.2
Median	19	26	18
% No nausea	41	41	41
Investigator's assessment of maximum nausea†			
n	163	161	149
Mean ± S.E.M.	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
Median	1	1	1
% No nausea	43	44	42

*Patients' most severe episode of nausea rated according to a 100 mm visual analogue scale (VAS) ranging from 0 = "none" to 100 = "nausea as bad as it can be." †Nausea rated according to a scale of 0 = none, 1 = slight, 2 = moderate, and 3 = severe.

*Table 4. Incidence of adverse events reported by ≥3% of patients**

Adverse event	Dolasetron mesilate 1.8 mg/kg (*n* = 163)	Dolasetron mesilate 2.4 mg/kg (*n* = 161)	Granisetron 3 mg (*n* = 150)
Headache	45 (28%)	36 (22%)	34 (23%)
Diarrhoea	21 (13%)	17 (11%)	9 (6%)
Abdominal pain	9 (6%)	1 (1%)	4 (3%)
Epigastric pain	4 (2%)	2 (1%)	4 (3%)
Hypertension	3 (2%)	11 (7%)	6 (4%)
Abnormal hepatic function	14 (9%)	9 (6%)	5 (3%)
Extrasystoles	5 (3%)	2 (1%)	1 (1%)
Asthenia	5 (3%)	1 (1%)	1 (1%)
Fever	3 (2%)	5 (3%)	4 (3%)

*Values represent number (%) of patients reporting an adverse event.

treatment. Further, there were no statistically different changes in QRS duration between the three treatment groups at hours 1–2 or 24. Overall, the acute changes observed in ECG parameters were small and did not translate into clinically important adverse cardiovascular events (Table 4). The cardiovascular events that could result (e.g. first degree AV block, sinus bradycardia, bundle branch block, sinus arrhythmia or extrasystole) from the observed ECG changes were small and similar for the three treatment groups.

Evaluation of vital signs revealed no evidence of an effect of treatment. Laboratory abnormalities were consistent with the patients' disease status, chemotherapy regimen and hydration status.

DISCUSSION

In this study, single i.v. doses of 1.8 and 2.4 mg/kg of dolasetron mesilate and 3 mg of granisetron were equally effective in preventing nausea and vomiting in cancer patients receiving high-dose (≥80 mg/m^2) cisplatin. Expressed as dolasetron base, these doses are 1.3 and 1.8 mg/kg, respectively. There were no significant differences between the treatment groups of any of the primary or secondary efficacy variables measured, although the 1.8 mg/kg dose of dolasetron mesilate produced numerically superior responses for most efficacy parameters compared to the 2.4 mg/kg dose. Patients were equally satisfied with the three treatment regimens.

Complete responses were achieved in 54% of patients in the dolasetron mesilate 1.8 mg/kg group, 47% of patients in the dolasetron mesilate 2.4 mg/kg group and 48% of patients in the granisetron group. The higher, but not significantly different, response rate in the dolasetron mesilate 1.8 mg/kg group was also reflected in the median time to first emetic episode or use of escape medication which was >24.00 h in the dolasetron mesilate 1.8 mg/kg group, compared with 22.21 h in the dolasetron mesilate 2.4 mg/kg group and 23.17 h in the granisetron group. This study confirms the results of a comparative study between dolasetron and ondansetron that also demonstrated no additional benefit with 2.4 mg/kg compared with 1.8 mg/kg of dolasetron mesilate [27]. These trends also are consistent with results from a dose-ranging study in cisplatin-induced emesis and vomiting by Kris and associates that demonstrated a plateau in the dose–

response curve at dolasetron mesilate doses above 1.8 mg/kg [18]. The complete response rates in this study were similar to the complete response rates of 55 and 48% reported by Yeilding and associates [21] and by Harman and colleagues [20], respectively, in earlier trials with a single i.v. dose of 1.8 mg/kg of dolasetron mesilate in the prevention of cisplatin-induced emesis. In addition, in a comparative study with metoclopramide in cisplatin-treated patients, Chevallier and associates [28] recently reported that complete responses were achieved by 57% of patients who received a single i.v. 1.8 mg/kg dose of dolasetron mesilate compared with only 35% for patients given metoclopramide. The complete response rates observed in this study were also consistent with rates reported for other single-agent 5-HT_3 antagonist regimens in patients undergoing highly emetogenic chemotherapy [5,29,30].

The effectiveness of anti-emetic agents in controlling chemotherapy-induced nausea and vomiting has been shown to vary not only according to the anti-emetic regimen but also according to the characteristics of the patients. Chemotherapy-induced nausea and vomiting may be more severe or difficult to prevent in female patients [6,15,29] and in patients who have had prior chemotherapy [4,15]. To control for these factors, the patients in this study were stratified by gender and prior experience with chemotherapy before randomisation. Indeed, in all three treatment groups, the rate of complete response was significantly greater among males than females, and among patients naive to chemotherapy than patients who has previously undergone chemotherapy. The efficacy of both treatments decreased when the risk factor increased from male naive patients to female non-naive patients. In addition, chemotherapy-induced emesis has been reported to be more easily controlled in patients with a history of chronic alcohol use [4, 6]. The treatment groups in our study were comparable at baseline with respect to this characteristic. The results of subgroup analyses were consistent with earlier observations and indicated that significantly greater efficiency was achieved in patients with a history of alcoholism.

The severity of chemotherapy-induced emesis is related to the type and dose of chemotherapy administered [6]. High-dose cisplatin therapy was chosen for the study because it is an effective antineoplastic agent, because it is highly emetogenic in all patients if effective anti-emetic therapy is not given, and because anti-emetic agents effective against cisplatin-induced emesis are also at least as effective against other cytotoxic therapies with lower emetogenicity [4]. In our study, subgroup analyses showed no significant difference between subgroups of patients receiving cisplatin doses of ≤ 90 mg/m^2 or >90 mg/m^2. It is interesting to note that in subgroups of patients treated with cisplatin in doses >90 mg/m^2, a complete response was noted in 59% of patients in the dolasetron mesilate 1.8 mg/kg group, compared with only 44% in the dolasetron mesilate 2.4 mg/kg group and 49% in the granisetron group.

Doses of 1.8 and 2.4 mg/kg of dolasetron mesilate were well tolerated in this patient population. The most frequently reported adverse event was headache, as is commonly the case with these and other 5-HT_3 receptor antagonists [4,6,25,30,31]. These findings were consistent with the results of other studies of dolasetron [15,16,18,20,32] and granisetron [23,33]. Asymptomatic, treatment-emergent ECG effects were observed in all three treatment groups. The minor increases in QRS duration, and PR and QT_c intervals noted among dolasetron-treated patients in this study were consistent with previous observations [16,18,32]; their appearance were also consistent with the time at which plasma concentrations are highest for dolasetron's active metabolite, MDL 74,156. A recent study reported on potential treatment-emergent ECG changes and other cardiac side-effects with granisetron [34]. The ECG changes observed in our study were small in magnitude and consistent with the electrophysiologic properties of these agents. In addition, the observed asymptomatic ECG changes were not associated with clinically significant adverse cardiovascular events. The incidence of treatment related cardiovascular events (e.g. first degree AV block, sinus bradycardia, bundle branch block, sinus arrhythmia or extrasystole) that could be expected to result from the observed ECG increases was small and similar for all treatment groups. Therefore, the changes in cardiac electrophysiology observed in this study were not of clinical significance and treatment with dolasetron and granisetron did not result in increased cardiovascular risk.

The results of this study indicated that single i.v. doses of 1.8 and 2.4 mg/kg of dolasetron mesilate were as effective as 3 mg of granisetron in preventing chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin-containing chemotherapy. There were no significant differences between the response rates achieved by the three groups, but the 1.8 mg/kg dose of dolasetron mesilate was numerically superior to the 2.4 mg/kg dose. No differences were observed between the groups regarding the patients' satisfaction with treatment. Moreover, the effectiveness of the treatments was statistically similar within each of the four patient strata evaluated. Gender, prior experience with chemotherapy and history of heavy alcohol use were all predictive of response. Responses to treatment were better in male patients, in patients naive to chemotherapy and in patients with a history of alcohol abuse. For all the endpoints, there was no additional benefit with 2.4 mg/kg of dolasetron mesilate compared with 1.8 mg/kg. In conclusion, single i.v. doses of 1.8 and 2.4 mg/kg of dolasetron mesilate (1.3 and 1.8 mg/kg, respectively, expressed as the base) had equally effective anti-emetic efficacy as a single 3 mg dose of granisetron and were well tolerated in patients receiving highly emetogenic chemotherapy. In addition, because no additional benefit was observed with 2.4 mg/kg of dolasetron mesilate and numerically greater responses were observed with the 1.8 mg/kg dose, the lower dose of 1.8 mg/kg is optimal for further clinical development.

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