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A Double-blind, Randomised, Crossover Comparison of Granisetron and Ondansetron in 5-day Fractionated Chemotherapy: Assessment of Efficacy, Safety and Patient Preference

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We report the first double-blind, randomised, crossover study comparing granisetron and ondansetron as antiemetics in cancer chemotherapy. Patients receiving two cycles of identical chemotherapy fractionated over 5 days were given either granisetron (3 mg/day) or ondansetron (24 mg/day) on each day of chemotherapy, using a double-dummy technique to preserve study blindness. Patients then crossed over to the other therapy. 309 patients (237 male) completed the crossover: 260 received cisplatin (mean dose 19.2 mg/m²/day) and 49 received ifosfamide (mean dose 1415 mg/m²/day). Primary efficacy variables were prospectively defined as complete response (no vomiting and mild or absent nausea) over 5 days, and patient preference. Both agents achieved good control of emetic symptoms with 5-day complete response rates of 44.0% on granisetron and 39.8% on ondansetron [95% confidence interval (CI) for odds ratio 0.8, 1.9]. Complete response rates were very similar in patients receiving either cisplatin (40.8% granisetron, 37.6% ondansetron) or ifosfamide (61.2% granisetron, 51.0% ondansetron). There was a statistically significant difference in patient preference in favour of granisetron, 105 patients preferred granisetron, 79 preferred ondansetron, 121 had no preference ($P = 0.048$: 95% CI for odds ratio 1.00, 1.84). Single daily doses of granisetron (3 mg/day) appeared similarly effective and well tolerated to three daily doses of ondansetron (8 mg three times daily) in prevention of emesis induced by 5-day fractionated chemotherapy, however, significantly more patients preferred granisetron.

Key words: granisetron, ondansetron, fractionated chemotherapy, emesis, patient preference
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INTRODUCTION

POWERFUL CHEMOTHERAPEUTIC agents, such as cisplatin and ifosfamide, are associated with multiple, potentially serious, side-effects including emesis, bone marrow suppression and nephrotoxicity, many of which are related to chemotherapy dose. Dividing the dose and spreading the cytotoxicity over several days (i.e. fractionating) can reduce toxicity whilst maintaining therapeutic efficacy. These fractionated chemotherapy regimens are in common use for specific tumour types such as testicular germ cell tumours [1], achieving cure rates in excess of 90% [2]. Despite administration of lower daily chemotherapy doses, nausea and vomiting occur in up to 100% of patients treated with these regimens [3]. Inadequate control of these symptoms can result in poor compliance with further curative treatment, as well as other distressing and hazardous complications such as malnutrition and dehydration [4]. All of these factors adversely impact on daily activities and detract from quality of life.

Conventional antiemetic treatments such as dopamine antagonists have met with limited success in this therapeutic setting.

Although high-dose metoclopramide is efficacious against cisplatin-based emesis through antagonism of 5-HT_3 receptors, effective doses are associated with extrapyramidal side-effects, which increase in frequency when treatment is administered over several consecutive days [5]. Moreover, these symptoms are particularly problematic in young adults [6, 7], a population in whom fractionated chemotherapy regimens are commonly used.

The new class of selective 5-HT_3 antagonists have particular utility, being highly effective as single agents, without risk of extrapyramidal side-effects or sedation. In patients undergoing fractionated chemotherapy, single daily doses of granisetron (SmithKline Beecham Pharmaceuticals, Reigate, U.K.) were superior to combinations of either high-dose metoclopramide plus dexamethasone or alizapride plus dexamethasone in terms of both efficacy and tolerability [8, 9]. Ondansetron (Glaxo Pharmaceuticals, U.K.) has shown superiority over high-dose metoclopramide as a single agent in patients undergoing multiple day cisplatin-based regimens [10]. Differences are emerging in the preclinical profiles of granisetron and ondansetron; granisetron is more potent, longer acting and more selective for the 5-HT_3 receptor subtype, with a more conventional dose–response profile [11]. An open clinical study comparing these two agents reported a significantly lower incidence of failure (> two vomits) following granisetron and patient preference ratings also favoured granisetron [12].

The present double-blind, double-dummy study directly compared the efficacy and safety of granisetron and ondansetron in cancer patients receiving their first course of fractionated chemotherapy and assessed patient preference for the two treatments. Single daily intravenous doses of granisetron (3 mg) were compared with three daily intravenous doses of ondansetron (8 mg three times daily). This is the first large randomised double-blind, crossover comparative study of these two agents to be reported.

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PATIENTS AND METHODS

Patient population

This was a multicentre, randomised, double-blind, double-dummy, crossover study. Chemotherapy-naive patients, who were due to receive either 5-day fractionated regimens containing cisplatin (≥ 15 mg/m²/day) or ifosfamide (> 1.2 g/m²/day) as primary treatment for malignant disease, were eligible for inclusion. Patients with marked hepatic dysfunction, congestive heart failure, active peptic ulcer, gastrointestinal obstruction, primary or secondary brain tumours, or pre-existing acute or chronic nausea and/or vomiting were excluded. With the exception of short-acting benzodiazepines, any change in medication with central nervous system (CNS) activity was not permitted, and concomitant treatment with corticosteroids or other anti-emetics was not allowed.

All patients gave informed consent to their participation in the study and were free to withdraw at any time. The study was performed in accordance with the Declaration of Hensinki (1964) revised in Tokyo (1975), and subsequent Venice (1983) and Hong Kong (1989) amendments. The approval of the protocol by an appropriate local Ethical Review Committee was also obtained.

Chemotherapy

Patients received two 5-day cycles of the same primary cytostatic treatment; either intravenous cisplatin ≥ 15 mg/m²/day for 5 days, or ifosfamide ≥ 1.2 g/m²/day for 5 days. Combination with other cytostatic agents given concomitantly was permitted.

Anti-emetic therapy

Patients were randomised to receive either a single intravenous dose of granisetron 3 mg/day or intravenous ondansetron 24 mg/day (8 mg three times daily) for 5 days. Study blinding was maintained using a double-dummy technique. Granisetron was administered as a single 15-min infusion, completed 5 min prior to chemotherapy each day. Ondansetron was given as three 15-min infusions of 8 mg each, the first finishing 5 min prior to chemotherapy and further doses being given at 8 and 16 h after the start of chemotherapy. Patients randomised to granisetron received placebo infusions at the 8- and 16-h time points. The same anti-emetic treatment regimen was followed on each day of the chemotherapy regimen for 5 days. During the second 5-day cycle of chemotherapy, patients received the alternative anti-emetic treatment.

Patients who experienced breakthrough nausea and/or vomiting on any chemotherapy day received up to two further blinded doses of granisetron 3 mg intravenously (patients receiving granisetron) or placebo granisetron (patients receiving ondansetron). Any subsequent uncontrolled nausea and vomiting was treated with a standard anti-emetic of the physician's choice and the patient was withdrawn from the cycle. These patients were eligible for inclusion in the second treatment cycle.

Efficacy assessments

Patients remained in hospital for each of the 5-day chemotherapy cycles. Assessments of nausea and vomiting were made at 6-h intervals throughout both 5-day chemotherapy periods. Severity of nausea was rated by the patient as none, mild, moderate or severe. The numbers of episodes of vomiting or

retching were noted as none, one, two, three, four or more than four. The time of the first episode of vomiting or moderate/severe nausea was noted at each cycle. In addition, the requirement for additional rescue doses of study medication (granisetron or placebo) or other rescue anti-emetic therapy was recorded. At the end of the second cycle, patients stated whether they preferred the first treatment or second treatment or had no preference for one or other.

Clinical monitoring and laboratory tests

Blood pressure, heart rate and body temperature were recorded at screening, immediately prior to the anti-emetic dose and every 6 h throughout both treatment cycles. In addition, routine haematological and biochemical tests were performed at screening, prior to the start of chemotherapy and on day 5 of both cycles; a further laboratory and vital signs examination was performed at a follow-up visit 7 days after the second cycle. All adverse experiences occurring throughout the entire study period between screening and follow-up were recorded.

Statistical analysis

The principle objectives of this study were to compare granisetron and ondansetron in naive cancer patients receiving their first course of fractionated chemotherapy and to gain data on patient preference for anti-emetic treatment. A review of the literature suggested that a difference of greater than 20% may exist in 5-day response rates between the two compounds [13]. Calculation of the study sample size was based on a parallel group comparison of treatments at the first study cycle, assuming a baseline 5-day complete response rate of 44%. The study was planned to recruit a total of 300 patients (150 per group at cycle 1) sufficient to detect a 16% difference between groups in 5-day complete response rates at the first cycle at the 5% significance level and 80% power. The efficacy analysis was performed on an 'intention-to-treat' basis including all patients for whom at least one post-anti-emetic dose assessment was available. All patients were included in the safety analysis.

The primary variables of interest at the first study cycle were (i) complete response over 24 h and 5 days, i.e. no vomiting, no worse than mild nausea, no rescue treatment (either additional rescue doses of study medication or other rescue anti-emetics) and no withdrawal during the defined period, (ii) requirement for other rescue anti-emetics, (iii) time to first episode of moderate/severe nausea, vomiting and use of rescue (using Kaplan–Meier survival methods), (iv) clinician's global assessment of anti-emetic efficacy, and (v) incidence of adverse events. Patient preference data was collected by switching patients to the alternative anti-emetic treatment at the second cycle. Tests of statistical significance were conducted using the χ^2 test and Cox log rank test. In the absence of a treatment-by-cycle interaction, assessed using the Hills and Armitage test [14], a crossover analysis on patients completing both treatment cycles was also performed for the primary efficacy variables. The crossover analysis employed methods described by Kenward and Jones [15] for binary data and France, Lewis and Kay for survival data [16]. The Mainland–Gart test [17] was used to assess cycle and treatment effects and the Prescott's test was performed in addition to confirm that a consistent result was obtained [18]. All tests were performed at a 5% significance level (two-tailed).

Adverse experiences were analysed by frequency, severity and relationship to study drug. Experiences regarded as serious (defined as fatal, life-threatening, incapacitating or which resulted in hospitalisation, or overdose) were identified. Changes in laboratory parameters and vital signs were flagged if they exceeded a predetermined limit.

RESULTS

A total of 359 patients were recruited into the study from 46 centres in six countries between July 1991 and November 1992: Austria (n = 24), France (n = 207), Germany (n = 72), the Netherlands (n = 12), South Africa (n = 27) and the U.K. (n = 17). 176 patients received granisetron in cycle 1, of whom 154 went on to receive ondansetron in cycle 2. 183 patients received ondansetron in cycle 1 of whom 155 went on to receive granisetron in cycle 2. Thus, 309 patients were available for crossover analysis. The groups were well matched in terms of age, gender, weight and primary tumour site. The study population was predominantly male (77.4%) and the most common primary tumour sites were head and neck (25.3%), lung (18.1%) and testes (16.7%). Demographic characteristics for patients participating in either cycle are provided in Table 1. Most patients received cisplatin chemotherapy (84%) at a mean dose of approximately 19 mg/m^2/day, or a total dose of 95 mg/m^2 per cycle (Table 2).

Efficacy

The efficacy of granisetron and ondansetron, in terms of complete response rates (no vomiting or worse than mild nausea), no vomiting rates and failure rates (> four vomits) during the first 24 h and over 5 days at both cycles, are presented in Table 3. Over the first 24 h at cycle 1, approximately 90% of patients in both groups were complete responders and only 2% on either treatment were failures during this period. Over the entire 5-day period in cycle 1, complete response was achieved in almost 40% of patients in both groups and the proportion of failures was also similar between groups. There was no significant difference

Table 1. Key demographic characteristics

	Granisetron	Ondansetron
Cycle 1		
Number enrolled	176	183
Males/females	136/40	142/41
Mean weight (kg)	66.9	67.9
Range	(39–118)	(38–114)
Mean age (years)	51.0	52.6
Range	(20–79)	(18–83)
Primary site (n)		
Head and neck	39	52
Lung	31	34
Ovary/cervix	17	10
Testis	34	26
Other	55	61
Cycle 2		
Number enrolled	155	154
Males/females	118/37	119/35
Mean age (years)	52.1	51.4
Range	(18–83)	(22–78)
Primary site (n)		
Head and neck	49	37
Lung	25	26
Ovary/cervix	8	15
Testis	21	29
Other	52	47

Table 2. Chemotherapy received and dose (mg/m²/day)

	Granisetron	Ondansetron
Cycle 1		
Number received cisplatin	151	148
Dose: mean (range)	19.3 (14.7–37.9)	19.2 (11.3–31.4)
Number received ifosfamide	25	35
Dose: mean (range)	1406 (1018–2455)	1382 (1030–2021)
Cycle 2		
Number received cisplatin	128	132
Dose: mean (range)	19.3 (13.5–36.2)	19.0 (11.9–25.3)
Number received ifosfamide	27	22
Dose: mean (range)	1460 (1097–3930)	1374 (1018–2006)

Mean relates to day 1; range relates to days 1–5.

between groups in complete response rates at 24 h or over 5 days; there was also no evidence to suggest that complete response rates differed significantly between countries. The percentage of patients receiving additional rescue doses of study medication on any day ranged from 3.4% (day 1) to 17.4% (day 4) on granisetron and from 4.4% (day 1) to 18.7% (day 4) on ondansetron. At the second cycle, 5-day efficacy parameters (complete response, no vomiting and failure rates) all showed a small advantage for granisetron but failed to achieve statistical significance.

When data from both treatment sequences were combined, the overall percentage of patients attaining complete response over 5 days was 44.0% for granisetron and 39.8% for ondansetron. The 5-day complete response rates in the subgroups receiving cisplatin or ifosfamide are presented in Table 4. The times to first vomiting episode and first use of rescue were significantly longer in cycle 1 than cycle 2 ($P = 0.029$ and $P = 0.036$, respectively) and approached significance for time to first episode of moderate or severe nausea ($P = 0.074$).

Table 4. Five-day efficacy results for treatment sequences combined

Complete response	*n*	Granisetron (%)	Ondansetron (%)	95% CI for odds ratio
All patients	309	44.0	39.8	(0.82, 1.86)
Cisplatin group	260	40.8	37.6	(0.75, 1.85)
Ifosfamide group	49	61.2	51.0	(0.61, 4.08)

Patient treatment preference

Of the group receiving granisetron in cycle 1 and ondansetron in cycle 2, 68 (44.2%) preferred granisetron, 25 (16.2%) preferred ondansetron and 59 (38.3%) were undecided. In patients receiving ondansetron at cycle 1 followed by granisetron at cycle 2, 37 (23.9%) preferred granisetron, 54 (34.8%) preferred ondansetron and 62 (40.0%) were undecided. When the two treatment sequences were combined, 105 patients (34.0%) preferred granisetron, 79 (25.6%) preferred ondansetron and 121 (39.2%) were undecided (data unavailable for 4 patients) [$P = 0.048$; 95% confidence interval (CI) for odds ratio 1.00, 1.84]. Patient preference for the treatment given at cycle 1 was also significantly greater than for treatment given at cycle 2 ($P < 0.001$). (Note: the Mainland–Gart test for treatment effect is valid in the presence of the observed cycle effect; a consistant result was obtained with Prescott's test.)

The data were examined to investigate any association between preference for a particular treatment and efficacy or safety (Table 5). The data suggest that an association exists between 5-day complete response rates and preference for one or other treatment. In patients expressing no preference, the 5-day complete response rates were similarly high after both treatments. In patients stating a preference for one particular treatment, 5-day complete response rates were considerably lower with the other compound. No clear association was established between the incidence of adverse events and patient preference.

Table 3. Efficacy results by cycle

	Granisetron	Ondansetron	95% CI for difference
Cycle 1			
24 h efficacy			
% complete response	91.5	89.1	(−3.7%, 8.5%)
% no vomiting	94.9	90.7	(−1.1%, 9.5%)
% failure (> four vomits)	2.3	2.2	(−3.0%, 3.1%)
5-day efficacy			
% complete response	39.2	37.3	(−8.8%, 11.5%)
% no vomiting	44.3	45.4	(−11.4%, 9.4%)
% failure (> four vomits)	20.5	21.3	(−9.3%, 7.5%)
Cycle 2			
24 h efficacy			
% complete response	82.6	86.4	(−11.8%, 4.3%)
% no vomiting	86.5	87.0	(−8.1%, 7.0%)
% failure (> four vomits)	2.6	4.5	(−6.1%, 2.2%)
5-day efficacy			
% complete response	46.5	40.3	(−4.8%, 17.2%)
% no vomiting	50.3	44.8	(−5.6%, 16.6%)
% failure (> four vomits)	21.3	25.3	(−13.5%, 5.4%)

Table 5. Relationship between patient preference and efficacy response rates

Preferred treatment	*n*	5-day complete response rate Granisetron (%)	Ondansetron (%)
Granisetron	105	48.6	19.2
Ondansetron	79	13.9	46.8
Undecided	121	60.8	54.6

Data unavailable for 4 patients.

Withdrawals

The numbers of patients withdrawing at each study cycle were similar between the two groups. Only 5% of patients in both groups discontinued treatment due to poor anti-emetic efficacy at cycle 1. The percentages withdrawing from cycle 2 due to lack of efficacy were 5.2 and 7.8% for granisetron and ondansetron, respectively. Fewer than 3% of patients in both groups withdrew from study treatment at either cycle due to adverse events.

Safety—adverse events

The most commonly occurring adverse events in each study cycle are shown in Table 6. The percentage of patients experiencing adverse events were similar between treatment groups in each cycle. Adverse events occurring with the highest frequency in both groups at each cycle were headache and constipation. The pattern of adverse events was similar between groups in both cycles and there were no statistically significant differences in the incidence of any individual adverse event.

11 patients in each group had adverse events classified as serious at cycle 1; the number with serious adverse events during cycle 2 was six and seven for granisetron and ondansetron groups, respectively. A total of 6 patients died in the granisetron groups (3 at first cycle, 3 at second cycle). There were 7 patient deaths in the ondansetron groups (6 at first cycle, 1 at second cycle). The majority of serious events and deaths in both groups were related to the co-administered chemotherapy and underlying disease. There were no marked differences between groups in the incidence of abnormal laboratory parameters or vital signs post-treatment.

Table 6. Most frequently occurring adverse experiences in cycles 1 and 2

	Cycle 1		Cycle 2	
	Granisetron *n* = 176 %	Ondansetron *n* = 183 %	Granisetron *n* = 155 %	Ondansetron *n* = 154 %
Any experience	67.6	67.8	56.1	58.4
Constipation	19.9	18.0	9.0	14.3
Headache	18.2	19.1	10.3	14.9
Pain	14.8	12.0	8.4	7.8
Insomnia	5.1	6.0	4.5	2.6
Hypertension	4.5	6.0	6.5	6.5
Diarrhoea	4.5	7.7	4.5	7.8
Decreased appetite	2.8	6.0	2.6	1.3

DISCUSSION

Although differences in the preclinical pharmacology of granisetron and ondansetron have been demonstrated [11], the clinical relevance of these findings is not clear. It is difficult to draw conclusions about the relative clinical efficacy of the two agents from the published literature, due to differences in methodology and the criteria employed for assessment. A recent clinical comparison suggested, however, that clinical differences may exist. Jantunen and colleagues [12] compared single doses of granisetron (3 mg i.v.), ondansetron (8 mg i.v.) and tropisetron (5 mg i.v.) in 130 patients in a crossover design study. Granisetron was favoured by patients over the other two agents and was associated with a significantly lower incidence of failure (> two vomits). The study, however, had some limitations, since it was open and nausea was not assessed. Additionally, the majority of patients were female, receiving cyclophosphamide-based regimens.

The present study compared single doses of granisetron against three doses of ondansetron in a randomised double-blind crossover design study. Although crossover designs have been criticised because the outcome at one cycle can influence response at the next cycle, they do offer a valid alternative to parallel study designs, since they are not subject to wide interpatient variations and additionally permit patient preference to be assessed. In fact, there was no evidence in this study that response at the first cycle did affect outcome at the second cycle. In contrast to the Jantunen study, the majority of patients were male receiving cisplatin regimens fractionated over 5 days.

Nausea and vomiting assessments demonstrated that both compounds were effective for the prophlaxis of emesis induced by 5-day fractionated cisplatin and ifosfamide regimens. At the first cycle, 5-day complete response rates of around 40% were achieved following either compound. Emesis associated with multiple-day cisplatin regimens is most severe on the first day; a mean of 10 vomits can be expected during this period without adequate anti-emetic protection [19]. It is, therefore, particularly impressive that 90% of patients in both groups were completely free of vomiting and significant nausea during the initial 24 h. At the second cycle, there was a trend in favour of granisetron in 5-day complete response rates (46.5 versus 40.3%). Additionally, when treatment sequences were combined, a small advantage for granisetron over ondansetron was seen (44.0 versus 39.8%). However, no statistically significant differences were detected between the two agents in any nausea or vomiting assessments over 24 h or 5 days. Responses to both treatments during the first 24 h were generally higher at the first cycle than at the second and this was accompanied by a later onset of vomiting at the first cycle. However, there was no apparent reduction in 5-day efficacy response rates at the second cycle compared with the first. There were no marked differences in the side-effect profiles between compounds.

In addition to assessments of efficacy and safety, the two compounds were compared in terms of the global variable of patient preference. A proportion of patients (40%) stated no particular preference for one or other anti-emetic. However, of the remaining 60% of patients, significantly more expressed a preference for granisetron (34%) over ondansetron (26%) ($P < 0.05$). In the absence of marked differences in the efficacy or tolerability of the two compounds, this finding was investigated further to identify the origin of the preference. The analysis revealed that 5-day complete response rates on the two treatments were similarly high (around 55–60%) in the subgroup expressing no preference. In the two sub-groups stating a

preference, 5-day complete response rates were considerably higher on the preferred treatment (around 50%) compared with the alternative treatment (less than 20%). This suggests that patient preference for one particular treatment was largely driven by sub-optimal therapeutic response on the other treatment and confirms the power of preference assessment in discriminating between two compounds of apparently comparable efficacy [20]. The significant preference for granisetron was, therefore, probably related to the lower 5-day complete response rate with ondansetron, although the observed difference in efficacy was small (44 versus 40%) and did not reach statistical significance. There was no evidence to suggest that patient preference was influenced by differences in the safety profile between compounds.

The results of this study confirm previous findings of Jantunen and colleagues [12] and imply that patients favour granisetron over ondansetron, regardless of their gender or the type of chemotherapy received. Granisetron and ondansetron are used in cancer treatment to ameliorate the emetic side-effects of chemotherapy and thus improve the patient's quality of life. In this context, and especially in the absence of any major differences in safety, patient preference is a most important determinant of the relative utility of the two treatments. It is also important to note that patient preference was not influenced by the administration schedule of the two drugs because of the double-dummy technique employed.

In conclusion, single daily doses of granisetron were as effective as three daily doses of ondansetron in the prevention of nausea and vomiting associated with 5-day fractionated chemotherapy. For patients who stated a preference, granisetron was favoured by significantly more patients.

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