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Acknowledgements—This study was supported by Sigrid Juselius Foundation.

Eur J Cancer, Vol. 29A, No. 1, pp. 33–36, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

A Randomised, Double-Blind Comparison of Granisetron with High-dose Metoclopramide, Dexamethasone and Diphenhydramine for Cisplatin-induced Emesis

An NCI Canada Clinical Trials Group Phase III Trial

David Warr, Andrew Wilan, Peter Venner, Joseph Pater, Leonard Kaizer, Francis Laberge, Jean Latreille, David Stewart, Gregory O'Connell, David Osoba, Kenneth Wilson, Alan Davis and Dianne Johnston

151 patients (149 evaluable) receiving their first course of chemotherapy containing cisplatin in a dose of at least 50 mg/m^2 were randomised to receive either a single dose of intravenous granisetron 80 μg/kg or intravenous metoclopramide 2 mg/kg every 2 h for five doses plus a single dose of dexamethasone 10 mg and diphenhydramine. After 24 h, there was no significant difference between groups with respect to nausesa or vomiting: in the granisetron group 46% of patients had no emesis, versus 44% of the standard group. Granisetron is an antiemetic agent with efficacy similar to that of high-dose metoclopramide plus dexamethasone.
Eur J Cancer, Vol. 29A, No. 1, pp. 33–36, 1993.

INTRODUCTION

CISPLATIN IS the most emetogenic cytotoxic agent [1]. The use of high-dose metoclopramide in combination with dexamethasone has decreased the frequency and severity of emesis [2–4] but a majority of patients will still vomit following therapy [5]. In addition, the adverse effects of restlessness and extrapyramidal symptoms due to dopamine receptor antagonism continue to be troublesome for some patients despite the use of diphenhydramine of lorazepam [6]. Thus there is a need for more effective, better tolerated antiemetics.

The hypothesis by Miner and Sanger that the antiemetic effect of metoclopramide might be due to an antagonistic effect at the 5-HT$_3$ receptor led to the discovery of a novel class of antiemetics that were remarkably effective in animals [7]. In patients with cancer, a recent double-blind study showed that a single dose of the selective 5-HT$_3$ antagonist granisetron was markedly superior to dexamethasone and prochlorperazine for moderately emetogenic chemotherapy [8]. There was prevention of emesis in 70% of patients with very little breakthrough beyond 12 h suggesting that additional administration of granisetron was not required. The only published comparative study for cisplatin-induced emesis thus far is a single-blind study by Chevallier *et al.* in which granisetron provided protection from cisplatin-induced emesis that was equivalent to an 8 h metoclopramide infusion plus dexamethasone [9].

The objective of this study was a double-blind comparison of the antiemetic activity of a single injection of granisetron with a standard therapy which, by consensus of the investigators, was an intermittent schedule of high-dose metoclopramide plus dexamethasone and diphenhydramine.

PATIENTS AND METHODS

Entry criteria

Patients were considered eligible if they were at least 18 years of age, spent less than 50% of the daytime in bed (Eastern Cooperative Oncology Group performance status < 3), had no

Table 1. Trial design: randomisation to either standard therapy or granisetron

Standard therapy:	Diphenhydramine 10 mg intravenously × 1 metoclopramide 2 mg/kg intravenously every 2 hours × 5 dexamethasone 10 mg intravenously × 1
Granisetron:	80 μg/kg intravenously × 1 plus matching placebos

prior chemotherapy and were to receive cisplatin in a dose of at least 50 mg/m^2 with a minimum in-hospital stay of 12 h.

Exclusion criteria were: nausea or vomiting within the previous 7 days, bowel obstruction, brain metastases, impaired cardiovascular status (congestive heart failure, uncontrolled angina, uncontrolled arrhythmias), serum creatinine ≥ 120 mol/l, liver function tests [aspartine aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDM), glutamyltranspeptidase (gamma-GT), or bilirubin] greater than twice the upper limit of normal or concurrent therapy with corticosteroids, benzodiazepines, butyrophenones, cannabinoids, tricyclic antidepressants or monoamine oxidase inhibitors. Written consent was obtained from all patients who entered the study.

Pretreatment evaluation

Pretreatment evaluation included a complete history and physical examination, complete blood count, biochemistry [AST, ALT, LDH, gamma-GT, bilirubin, alkaline phosphatase, sodium, potassium, blood urea nitrogen (BUN), creatinine, globulin, albumin] complete urinalysis and an electrocardiogram. All data regarding nausea and vomiting were derived from patient-completed scales in the form of a 3 day diary. Visual analogue scales (VAS) were used to assess baseline anxiety, nausea, and drowsiness. Categorical scales were used to assess baseline emesis/retching and food intake.

Randomisation and drug administration

Randomisation was carried out centrally by the NCI Canada Clinical Trials Group office with stratification by centre and by the dose of cisplatin (< 75 mg/m^2 vs. ≥ 75 mg/m^2). For drugs doses and schedule, see Table 1. Matching placebos were given in the granisetron group to maintain 'blinding' of the patient, nurse and physician.

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Revised 29 June 1992; accepted 1 July 1992.

Outcome assessment

The major endpoints of this study were nausea and emesis or retching over the first 24 h post chemotherapy. Nausea and vomiting/retching were assessed by patient self-report using a 3-day diary that had been validated in a previous anti-emetic study [10]. Severity of nausea was assessed with a 100 mm VAS with the words "no nausea" and "extremely severe nausea" appearing at opposite ends. A similar scale for nausea duration with the anchors "none of the time" and "all of the time" was used. Patients were asked to record the number of episodes of retching or vomiting on a five-point categorical scale (0, 1–2, 3–5, 6–10, 11 or more times). These scales were filled out by the patient at 6-h intervals for the first 24 h. Food intake was assessed by a categorical scale ("much less than usual, less than usual, about the same as usual, more than usual") at 24-h intervals for all 3 days.

On two occasions (3 h and 4–7 days post chemotherapy) patients were asked whether or not the treatment (chemotherapy or antinausea therapy) had upset them in any way. The baseline blood work was repeated at 3 h and 4–7 days post chemotherapy.

Statistical considerations

The major outcome upon which sample size was based was the VAS for severity of nausea. It was calculated that a total of 150 patients would provide an 82% chance of achieving significance if the antiemetics differed by 10 mm VAS using the 2-sided 5% level test.

Logarithms of the scales for duration and severity of nausea were taken prior to analysis to remove positive skewing, and significance testing was carried out using analysis of covariance. Frequency of vomiting/retching scales were dichotomised to "no" vs. "some" retching or vomiting and analysed by the Mantel–Haensel method or logistic regression (depending upon whether the covariates were nominal or continuous).

The principal efficacy outcomes were the mean nausea score on the VAS over the first 24 h and the proportion of patients free of emesis after 24 h. For patients receiving more than one day of chemotherapy, efficacy results were censored at 24 h. All P values are 2-sided and adjusted for significant covariates.

RESULTS

Of the 151 patients randomised over 15 months, 2 were excluded from analysis because of withdrawal prior to receiving the study drugs. All patients who received a study drug were considered evaluable for adverse events. A secondary analysis was performed after excluding those patients (10 in the granisetron group and 12 in the control group) for whom there was either a major protocol violation or a co-intervention which might be anticipated to affect the outcomes of interest. Since the exclusion of these patients did not alter the conclusions, only data from the analysis carried out on all eligible patients will be presented.

There were no significant differences between the granisetron and standard therapy group in pretreatment characteristics (Table 2). The pre-trial alcohol intake of patients was not recorded in this study.

Statistically significant covariates were age for the outcome of nausea and cisplatin dose for the outcome of vomiting (younger patients and higher cisplatin dose were associated with less favourable results—see Table 3). Patient sex and performance status were not significant covariates.

Table 2. Patients' characteristics

	Treatment	
	Granisetron	Standard therapy
Number eligible	74	75
Sex (M/F)	42/32	46/29
Median age	57	55
Mean cisplatin dose (mg/m^2)	75	76
One day regimens	55	62
Cisplatin–cyclophosphamide	25	26
Cisplatin alone	16	18
Cisplatin–vindesine	10	11
Other cisplatin combinations	23	20

Table 3. Relationship between cisplatin dose and freedom from emesis at 24 h

Cisplatin Dose	% Free of emesis at 24 h	
	Granisetron	Standard therapy
< 75 mg/m^2	53	54
≥ 75 mg/m^2	39	35

Nausea

Nausea severity and duration scores were highly correlated ($r > 0.9$ for all time periods) and so only the nausea severity scores are presented. The mean VAS scores for nausea severity over the first 24 h were similar in both groups ($P = 0.36$), see Fig. 1. The proportions of patients remaining free from nausea were 28% and 35% in the granisetron and standard therapy groups respectively ($P = 0.28$). There were, however, time-dependent differences between treatment groups. During the first 6 h, the granisetron group experienced significantly less nausea ($P < 0.033$) than the standard therapy group but in the 18–24 h interval, the reverse was true ($P = 0.013$). There was a trend towards greater nausea severity on day 2 with granisetron ($P = 0.053$) but not on day 3 ($P = 0.45$).

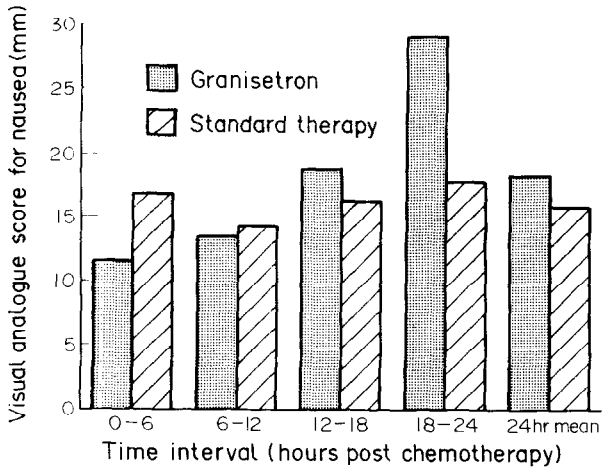

Fig. 1. Mean visual analogue scores for nausea severity at intervals over the first 24 h following antiemetic treatment with either granisetron or metoclopramide, dexamethasone and diphenhydramine.

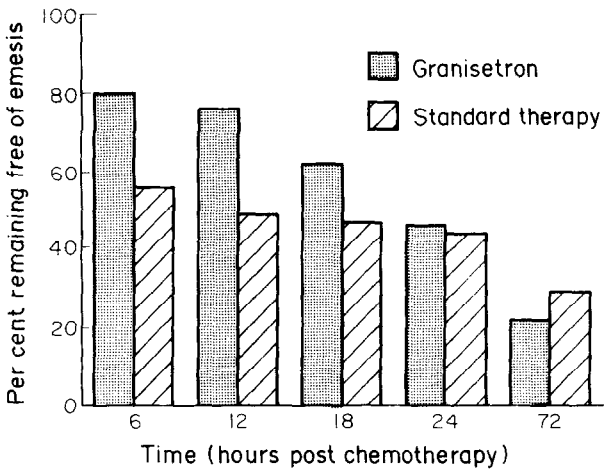

Fig. 2. Per cent of patients free of emesis over the 72 h study period following antiemetic treatment with granisetron or metoclopramide, dexamethasone and diphenhydramine.

Emesis/retching

During the initial 24 h 46% of the granisetron group and 44% of the standard therapy group experienced no emesis ($P = 0.44$), see Fig. 2. As with nausea, there was a significant difference over the initial 6 h in favour of granisetron but this difference disappeared after 24 h had elapsed. 22 patients in the granisetron group vs. 4 patients in the standard therapy group experienced their first episode of emesis or retching 12–24 h following antiemetic therapy. By 72 h, the proportion of patients remaining free of emesis and retching was 22% in the granisetron group vs. 29% in the standard therapy group.

Antiemetics were used for breakthrough emesis in 47% of the granisetron group and 33% of the standard therapy group ($P = 0.082$).

Adverse events

Both treatments were well tolerated. Table 4 lists the most frequently reported adverse events. There was significantly less somnolence with granisetron at 3 h post chemotherapy ($P = 0.003$) but a trend toward more headaches ($P = 0.067$). Restlessness and extrapyramidal reactions were infrequent. The frequency of mild, transient liver function abnormalities was similar in both groups.

DISCUSSION

This trial demonstrated that a single dose of granisetron is comparable in efficacy to the most effective combination

Table 4. Adverse events

	Treatment	
Adverse event	Granisetron	Standard therapy
Headache	17	8
Somnolence	11	22
Asthenia	11	14
Anxiety	11	9
Diarrhoea	11	8
Constipation	9	6
Agitation	7	9
Extrapyramidal symptoms	0	2

antiemetic therapy not involving specific 5-HT_3 receptor antagonists. The efficacy of granisetron was time-dependent with superior antiemetic efficacy to metoclopramide, dexamethasone and diphenhydramine over the first 12 h but equivalence by 24 h. Both types of antiemetic therapy were well tolerated. The use of diphenhydramine and the relatively high median age may account for the fact that restlessness was not very troublesome in subjects treated with metoclopramide. As would be expected, extrapyramidal effects were not observed with granisetron but this drug was associated with an increase in headaches of mild to moderate severity.

Although granisetron prevented the acute onset of emesis in approximately one half of the patients, its efficacy was most notable in the initial 12 h. A delayed onset of emesis with granisetron has also been noted by others [11]. Changes that one could consider to improve efficacy would include use of higher doses, repeat dosing and drug combinations.

Dose–response studies of granisetron in patients receiving cisplatin chemotherapy by Soukop *et al.* [11] and in patients receiving non-cisplatin chemotherapy by Smith [12]. These two large trials failed to show a difference between single doses of 40 and 160 μg/kg. Further increments in dose are, therefore, unlikely to improve efficacy.

The observation that frequently began 12–24 h post treatment in this study raises the question of whether a change in schedule might improve results. As has been noted by others, some of our patients also experienced an onset of emesis beyond 24 h [11, 12]. Both of these observations would be consistent with a hypothesis that failure is based upon inadequate concentration of granisetron due to drug clearance. Our previous results with granisetron given for moderately emetogenic chemotherapy, however, argue against this rationale [8]. In that study the chemotherapy consisted mainly of combinations containing doxorubicin and cyclophosphamide which would be expected to cause emesis later in onset than cisplatin yet there was virtually no loss of efficacy during the 12–24 h postchemotherapy. Thus the mechanism of emesis beyond 12 h may well be due to a cause other than declining levels of granisetron. Further studies are required to determine the value of repeat doses of granisetron both in the first 24 h and beyond.

The addition of antiemetic drugs that work by a different mechanism of action is a rational approach in efforts to improve results obtained with granisetron. Dexamethasone increases the complete protection rate of the nonspecific 5-HT_3 antagonist high-dose metoclopramide by 17–34% [2, 3, 13] and the selective antagonist ondansetron by more than 20% [14, 15]. It is probable that there would be similar benefit for the combination of granisetron and dexamethasone. The NCI Canada Clinical Trials Group is currently evaluating the benefit of adding this glucocorticoid to granisetron over the 7 days following cisplatin therapy.

We conclude that a single dose of granisetron is comparable in antiemetic efficacy to high-dose metoclopramide, dexamethasone and diphenhydramine but superior in its adverse effect profile and convenience of administration. Further studies are required to define the optimal way of using this new antiemetic.

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