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Original Article

A randomized trial of two doses of granisetron in the treatment of chemotherapy-induced emesis. Dutch results within a multinational study

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Granisetron is a new serotonin-receptor antagonist with considerable activity in preclinical models and early clinical studies against drug-induced nausea and vomiting. In a randomized, double-blind trial, two dose levels of granisetron were compared with regard to their efficacy and safety if given to patients receiving emetogenic chemotherapy with or without cisplatin. The present paper reports the Dutch experience with 125 patients included in this international trial. The two dose levels (40 and 160 μg/kg given once i.v. prior to chemotherapy) were equally effective in preventing acute emesis and nausea (within the first 24 h); in the group receiving cisplatin doses of 50 mg/m^2 or more, 39% of patients had a complete response (no vomiting and mild nausea at most), with a complete response rate of 82% in the patients receiving moderately emetogenic chemotherapy. Sixty-three percent of patients receiving highly emetogenic chemotherapy with a complete response within 24 h lost this response during the next 6 days, as did 20% of the other patients. Headache was the most frequently reported adverse event (18%), followed by constipation (6%) and dizziness (4%). All adverse events were mild and occurred equally frequently at both dose levels. Granisetron at 40 μg/kg i.v. given once is effective in the prevention of acute chemotherapy-induced emesis and nausea, in particular in patients receiving moderately emetogenic therapy. Neth J Med 1992;40:221–226.

Key words: Granisetron; 5HT3-antagonists; Chemotherapy; Emesis; Nausea

Introduction

Considerable progress has been achieved in the control of nausea and emesis induced by cytostatic cancer therapy with the application of dopamine antagonists such as metoclopramide and alizapride combined with corticosteroids and benzodiazepines. In spite of this improvement, at least 30% of patients still vomit and serious side effects of the anti-emetics themselves often occur, particularly in younger patients [1]. With the recognition of a new class of receptors in both

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peripheral and central pathways of emesis, inhibitors of 5-hydroxytryptamine (5-HT) or serotonin at the 5-HT3 receptor level have been introduced as promising new anti-emetic agents [2,3]. Studies in animals receiving cisplatin or cyclophosphamide have confirmed this action and in several human studies good efficacy and remarkably low toxicity have been observed [4–6]. In the present paper, the Dutch experience with one of the 5-HT3 receptor antagonists, granisetron, is reported. This is part of a multinational study [7,8] addressing questions of efficacy and safety of this agent when one of two doses was given to patients receiving emetogenic chemotherapy with or without cisplatin.

Patients and Methods

Patients

Patients with a malignant disease and aged over 15 yr were eligible for this study. They should not have received prior chemotherapy, and were being treated at their first course. Chemotherapy had to be clearly emetogenic and include cisplatin at a dose of ≥ 50 mg/m^2 (called "highly emetogenic") or cisplatin at a dose of < 50 mg/m^2 and/or one of the following drugs: carboplatin (≥ 300 mg/m^2), cyclophosphamide (≥ 600 mg/m^2), dacarbazine (≥ 350 mg/m^2), doxorubicin (≥ 40 mg/m^2 as a single agent or ≥ 20 mg/m^2 in combination), epirubicin (≥ 75 mg/m^2 as a single agent or ≥ 50 mg/m^2 in combination). These latter regimens are called "moderately emetogenic". Other cytostatics were administered concurrently as usual and all emetogenic chemotherapy had to be given on the first day. Patients with marked hepatic dysfunction (serum liver enzyme tests more than 4 times the upper limit), renal dysfunction (serum creatinine level more than twice normal), low serum potassium (< 3.0 mmol/l), uncontrolled cardiovascular disease, brain tumour or seizures within the last year were excluded. Also excluded were patients with pretreatment nausea, vomiting or conditions leading to impaired gastro-intestinal motility. All patients had to give written or witnessed informed consent.

Anti-emetic treatment

After stratification for the type of cytostatic treatment, patients were randomized to receive granisetron at a dose of 40 μg/kg or 160 μg/kg in a double-blind design. Just prior to chemotherapy, granisetron was given by infusion in 50 ml 0.9% NaCl in 30 min. If necessary, up to 2 additional i.v. doses of 40 μg/kg granisetron could be administered within the first 24 h. If this treatment failed to control the symptoms, other anti-emetics could be given.

Assessments

Before receiving chemotherapy, all patients were screened for eligibility, vital signs (i.e. pulse, blood pressure, and temperature), and underwent laboratory examinations (haematology, blood chemistry and urinalysis) and a 12-lead electrocardiogram. All patients were admitted to hospital for at least 24 h after starting chemotherapy. Laboratory tests were repeated just before and 24 h after the administration of granisetron. The patient's general condition, state of alertness and vital signs were objectively recorded by a nurse/observer (from 0–12 h every 2 h, from 12–24 h every 6 h). Nausea, vomiting and appetite were recorded every 6 h, in consultation with the patient on the following four-point scales: nausea (during the last 6 h), none, mild, moderate, severe; vomiting (during the last 6 h), none, 1 episode of vomiting, 2–4 episodes of vomiting, more than 4 episodes of vomiting; and appetite (during the previous 6 h), much better, better, same as last week, worse, much worse. All adverse events were recorded and the severity of the event and its relation to granisetron were assessed by the observer. Patients were asked to make subjective scorings of their symptoms of nausea, emesis and appetite on a patient diary card from 24 h after chemotherapy upto and including the 6th day. Laboratory tests were repeated on the 7th day after chemotherapy. All adverse events during the follow-up period were recorded. Efficacy of the two prophylactic doses of granisetron was compared using the number of responders and the duration of response. Re-

sponse criteria were defined as follows: Complete response = 0 emetic episodes and no or only mild nausea, Major response = 1 emetic episode and/or moderate or severe nausea, Minor response = 2–4 emetic episodes regardless of nausea score, Failure = > 4 emetic episodes.

Results

Between September 1988 and July 1989, 125 patients were enrolled. Patient characteristics are summarized in Table 1. Of all patients, 83 did not vomit and showed no or only mild nausea during the first 24 h after the start of chemotherapy, giving a complete response rate of 66%. For the initial granisetron dose of 40 μg/kg or 160 μg/kg, the CR rate was 65% and 68%, respectively (Fig. 1). This lack of dose-effect is also confirmed by the overall results for this study, with CR rates of 57 and 60% [7] and 76 and 80% [8], respectively, for highly and moderately emetogenic therapy. If the data were analysed according to the type of chemotherapy, granisetron was highly effective in patients receiving moderately emetogenic therapy (CR rate 82%); in the group with cisplatin doses of 50 mg/m^2 or more, 39% of patients achieved a complete response (Fig. 2). Again, in both groups of patients there was no difference in efficacy for the 2 initial dose levels. Because of this lack of difference between the 2 dosage groups with regard to anti-emetic response or patient characteristics (Table 1), all patients will be discussed together. In the moderately emetogenic group, 13 of 64 patients (20%) recording a CR in the first 24 h, recorded one or more episodes of vomiting during the subsequent

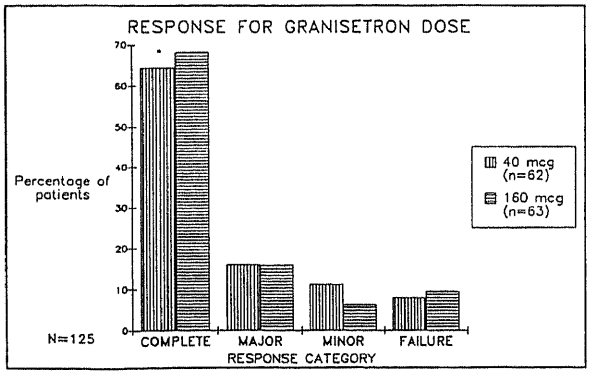

Fig. 1. Anti-emetic response rates in relation to dose of granisetron.

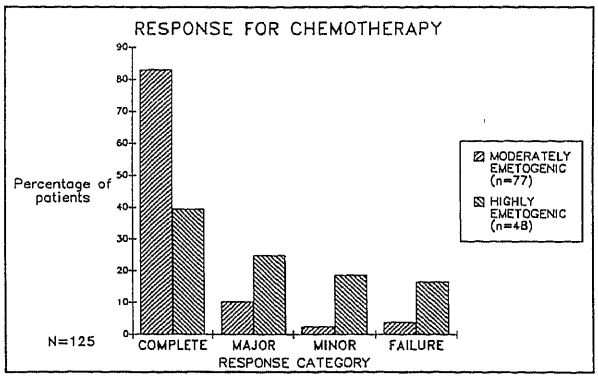

Fig. 2. Anti-emetic response rates in relation to type of chemotherapy.

TABLE 1

Patient characteristics

		40 μg/kg	160 μg/kg
Number of patients	125	62	63
males	60 (48%)	28	32
females	65 (52%)	34	31
age, mean	56	54	57
range	21–84	21–84	31–78
Primary site of tumour			
genitourinary	41 (33%)	19	22
lung	36 (29%)	18	18
breast	14 (11%)	7	7
haematological	18 (14%)	6	12
other	16 (13%)	10	6
Treatment			
highly emetogenic [1]	48 (38%)	24	24
moderately emetogenic	77 (62%)	38	39
Most frequent treatments			
CP [2]	22	10	12
CDE [3]	20	8	12
cisplatin only	12	7	5
CHOP [4]	11	4	7
CAF [5]	6	2	4

[1] For definition see text.
[2] Cyclophosphamide, cisplatin.
[3] Cyclophosphamide, doxorubicin, etoposide.
[4] Cyclophosphamide, doxorubicin, vincristine, prednisone.
[5] Cyclophosphamide, doxorubicin, 5-fluorouracil.

TABLE 2

Acute and delayed emesis after one day of granisetron treatment

Treatment [1]	Number of patients with			
	Acute emesis only [2]	Delayed emesis only [2]	Both	None
moderately emetogenic ($n = 77$)	3	13	10	51
highly emetogenic ($n = 48$)	0	12	29	7

[1] For definition see text.

[2] Delayed emesis: any emesis and/or moderate/severe nausea during days 1–6; acute emesis: any emesis and/or moderate/severe nausea during day 0.

6 days, and 23 (30%) of all patients had delayed emesis irrespective of their response on day 1 (Table 2). In contrast, 12 of 19 patients (63%) receiving highly emetogenic chemotherapy with a complete response in the first 24 h, vomited during the subsequent 6 days and 41 of 48 patients (85%) had delayed emesis irrespective of their response on day 1. For the majority of patients, control of emesis was obtained with only one dose of granisetron; 40% of patients in the 40 μg/kg group and 36% of patients in the 160 μg/kg group needed either one or two extra doses within the first 24 h.

The mean time from start of chemotherapy to the first rescue dose of granisetron was about 14 h. In most patients receiving one or two extra doses of granisetron their problems with nausea and/or emesis diminished or disappeared. Of 46 patients who received an extra dose of granisetron, problems of nausea and/of emesis were resolved in 14 patients, 24 showed some improvement and only 8 did not improve at all. Thirty-two patients of the highly emetogenic group ($n = 48$) were treated with an initial open dose of 40 μg/kg granisetron in their second and subsequent chemotherapy cycles. Sixty percent of patients who received a second cycle of cisplatin chemotherapy achieved at least a major response and this response appeared to be maintained in cycles 3, 4 and 5.

The safety profile was satisfactory: 48% of patients experienced no adverse events at all. The most frequently reported adverse event was headache (18%), followed by constipation (6%) and dizziness (4%). All these symptoms were mild and did not lead to refusal of a second treatment. No extrapyramidal symptoms were seen and laboratory tests were within the ranges expected for cancer patients treated with cytostatics. No hepatic transaminase elevations were noticed after granisetron administration. There was no apparent difference between the two dosage groups with regard to type and frequency of observed side effects.

Discussion

In our study, granisetron is an anti-emetic agent with an overall 24 h complete response rate of 66% and with at least a major response in 82% of patients. Single agent high-dose metoclopramide, currently the most frequently used dopamine receptor antagonist, has been found to prevent acute vomiting in 35% of patients receiving high-dose cisplatin [9,10] and in 40% of patients treated with regimens containing anthracyclines/cyclophosphamide [11]. In comparison with these data, 5HT3-antagonists such as granisetron appear to be a major improvement. For ondansetron, this has been substantiated in randomized trials in patients receiving anthracyclines/cyclophosphamide or cisplatin [11,12].

Extrapyramidal side effects are a major concern in the treatment of emesis with high-dose metoclopramide, particularly in younger patients. Frequencies as high as 10% have been reported [13,14]. In our study, granisetron was not found to be associated with these side effects. This finding is in accordance with a study comparing granisetron with high-dose metoclopramide plus dexamethasone [13].

Granisetron treatment, although more efficacious and less toxic than current anti-emetic treatments, still leaves a number of problems to be addressed. In particular, a considerable number of patients treated with high-dose cisplatin

still experience emesis. Based on the experience with dopamine receptor antagonists, combination anti-emetic treatment should be considered. In a number of studies, metoclopramide plus dexamethasone has been found to be superior to metoclopramide alone with 60% of cisplatin-treated patients having no emesis [15,16]. In two randomized studies, granisetron alone was found to be as effective as the combination of a dopamine antagonist and dexamethasone [13,17]. The combination of 5HT3 receptor antagonists with corticosteroids is currently under clinical investigation and may be a further step forward in anti-emetic control [18].

Delayed emesis remains a problem to be addressed. In our study, single day treatment with granisetron resulted in an overall delay in emesis in 51% of patients, including patients who had a complete response in the first 24 h. In the high-dose cisplatin-treated group this percentage was 85% and also included patients with adequate control of acute emesis; this result does not clearly differ from the incidence of delayed emesis after first-day treatment with metoclopramide plus dexamethasone [19]. Delayed emesis may contribute to the development of anticipatory vomiting in later courses of chemotherapy; also for this reason it is important to develop strategies to prevent it. Combining metoclopramide and dexamethasone was found to be superior in suppressing delayed emesis, compared to metoclopramide alone [20]. The addition of steroids to 5HT3 receptor antagonists may be similarly effective. Other possible modifications are the addition of benzodiazepines or prolongation of the administration of 5HT3 receptor antagonists by making use of their oral formulation [21].

In conclusion, we have confirmed the high anti-emetic activity of the 5HT3 receptor antagonist granisetron, which is associated with only mild adverse events. One might expect further improvement in the control of acute and delayed emesis by the addition of other agents such as steroids and benzodiazepines. This will make complete control of emesis a realistic perspective for the majority of patients, including patients treated with high dose cisplatin. Further trials in this area are currently in progress.

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