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GR38032F, a $5HT_3$ receptor antagonist, in the prophylaxis of acute cisplatin-induced nausea and vomiting

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Summary. A total of 28 patients receiving cancer chemotherapy with cisplatin-containing regimens (70–120 mg/m^2) participated in an evaluation of the efficacy and safety of GR38032F for the prevention of acute nausea and vomiting. GR38032F, a $5HT_3$ receptor antagonist, was given 30 min prior to cisplatin as an 8-mg loading dose by i.v. infusion over 15 min, followed by continuous infusion at a rate of 1 mg/h for 24 h. Efficacy was assessed by measurement of the number of episodes of retching and vomiting occurring in the 24 h after cisplatin administration and by an assessment of nausea during the same period. In all, 26 patients were evaluable for efficacy: overall, complete control was achieved in 12 patients (46%), major control (1–2 emetic episodes), in 6 (23%); minor control (3–5 episodes), in 1 (4%); control could not be achieved (failure; >5 episodes) in 7 patients (27%). GR38032F was well tolerated, with no significant drug-related adverse events. These encouraging results should be confirmed in comparative trials.

Introduction

Cisplatin is one of the most effective chemotherapeutic agents currently available but also one of the most emetogenic. Unless antiemetics are used nausea and vomiting occurs in all patients within 24 h following therapy with high-dose cisplatin [5, 7]. Although considerable advances have been made in the management of chemotherapy-induced emesis [11, 14, 15], current regimens are still not entirely effective for many patients receiving cisplatin or other highly emetogenic anticancer drugs. Antiemetics with dopamine antagonist activity can also induce extrapyramidal reactions, particularly in young patients [1].

5-Hydroxytryptamine M-receptors ($5HT_3$) have been identified in the gastrointestinal tract [9] and in the area postrema of the brain [10], and evidence for their role in the mediation of emesis has recently emerged [13]. Cisplatin is known to induce an increase in 5-hydroxytryptamine in the small intestine of the ferret [6], and emesis could be evoked by the activation of $5HT_3$ receptors in the peripheral nervous system. GR38032F is a highly selective $5HT_3$ receptor antagonist with no effect on dopamine receptors [2]. Given i.v. in doses of 0.1 and 1 mg/kg, GR38032F has completely abolished the emetic response to cisplatin in ferrets [3], the standard animal model. GR38032F has been shown to be an effective antiemetic when given as repeated short infusions in patients receiving cisplatin chemotherapy [12]. This pilot study was undertaken to establish whether GR38032F given as a continuous i.v. infusion over 24 h would be similarly effective in the prophylaxis of acute cisplatin-induced emesis.

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Materials and methods

Patients aged 18–70 years who were scheduled to receive their first course of anticancer chemotherapy (naive patients) with cisplatin-containing regimens (median dose, 86 mg/m^2; range, 70–120 mg/m^2) or who had previously received cisplatin were eligible for inclusion in this open study. Patients with severe concurrent illnesses other than neoplasia were ineligible; those who experienced nausea or vomiting or received antiemetics in the 24 h prior to chemotherapy were also excluded. Concurrent use of antiemetics rendered cases unevaluable. All participants gave oral informed consent, and the protocol was reviewed and approved by the Medical Ethics Committee of the Institut Curie, Paris.

The pretreatment assessment included a complete history, routine biochemistry (urea, creatinine, electrolytes, and liver-function tests), and hematology screening. GR38032F (the hydrochloride dihydrate salt of GR38032 base) was supplied by Glaxo Group Research Limited; 30 min prior to cisplatin, a dose of 8 mg diluted in normal saline to 50 ml was given as an i.v. infusion over 15 min. Immediately after this infusion was completed, a continuous 24-h i.v. infusion of GR38032F was given at a rate of 1 mg/h. Cisplatin was given by i.v. infusion over 1 h at doses of 70–120 mg/m^2, either alone or in combination with other cytotoxic drugs. Patients were monitored for 24 h following the administration of cisplatin; the timing and number of emetic episodes were recorded by an observer and cross-checked with the patients.

The control of emesis was graded overall as: complete, 0 emetic episodes; major, 1–2 emetic episodes; minor, 3–5 emetic episodes; and failure, >5 emetic episodes. Any vomiting that produced liquid was recorded as a single emetic episode; moreover, 1–5 retches (vomiting that did not produce liquid) within any 5-min period were also scored as a single emetic episode.

Table 1. Patient characteristics

Number of patients	28
Median age (range)	54 (18–66)
Median weight, kg (range)	62.5 (38–82)
Men : women	18:10
Primary site of cancer:	
Testes	6
Lung	5
Ovary	3
Uterus	3
Other	11
Naive patients	9
Previous cisplatin	19

Overall nausea was assessed by the patients using a 100-mm visual-analogue scale, with 0 mm representing "not at all sick" and 100 mm representing "worst ever feeling of sickness"; the difference between the end of treatment and pretreatment scores was recorded as the overall nausea score. At 24 h patients were asked, "If you were to receive chemotherapy again, would you want the same treatment to prevent nausea and vomiting?". The occurrence of any adverse events was noted; in particular, note was made of sedation, extrapyramidal reactions, and episodes of diarrhea. Sedation was graded as none, mild to moderate (easily rousable), or severe (rousable with difficulty). Routine biochemistry and hematology were repeated at 24 h and approximately 1 week later.

Results

A total of 28 patients (9 naive, 19 previously treated) were entered into this study; patient characteristics are presented in Table 1. Eight patients received cisplatin alone; the rest received cisplatin in combination with cyclophosphamide (11 patients), vinblastine (7), 5-fluorouracil (8), actinomycin D (6), doxorubicin (5), bleomycin (2), dacarbazine (2), etoposide (2), vindesine (2), ifosfamide (2), and methotrexate (1).

Efficacy

Two patients were excluded from the analysis of efficacy due to protocol violations: one received cisplatin at a dose of <70 mg/m^2, and the other received additional methylprednisolone during the study period. The efficacy of GR38032F is summarized in Table 2. A retrospective stratification, based on the respective dose of cisplatin as well as whether patients were receiving first or subsequent courses of treatment with cisplatin, is shown in Table 3. Overall, complete and major control of emesis was achieved in 18 of 26 (69%) patients.

In judging its acceptability as an antiemetic, 17 patients (65%) expressed a wish to receive GR38032F with further courses of chemotherapy, 1 (4%) did not want further courses, and 8 (31%) were not sure. Of the eight patients who were uncertain, five were receiving their first course of chemotherapy and therefore could not compare GR38032F with previous antiemetic treatment.

Table 2. Protective effect of GR38032F on cisplatin-induced nausea and vomiting

Response	*n*	Nausea (mm), median (range)
Complete (0)[a]	12 (46%)	0 (0–25)
Major (1–2)	6 (23%)	27 (1–52)
Minor (3–5)	1 (4%)	98
Failure (>5)	7 (27%)	69 (21–77)
Total	26	15 (0–98)

[a] Number of emetic episodes in the first 24 h after cisplatin

Table 3. Protective effect of GR38032F on cisplatin-induced nausea and vomiting, stratified for cisplatin dose and previous chemotherapy

Response	*n*	Nausea (mm), median (range)
Cisplatin dose, 70–99 mg/m^2 (naive patients)		
Complete	8 (89%)	1 (0–25)
Major	1 (11%)	1
Minor	0 (0%)	–
Failure	0 (0%)	–
Total	9	1 (0–25)
Cisplatin dose, 70–99 mg/m^2 (previously treated patients)		
Complete	3 (43%)	1 (0–10)
Major	3 (43%)	37 (33–52)
Minor	1 (14%)	98
Failure	0 (0%)	–
Total	7	33 (0–98)
Cisplatin dose, 100–120 mg/m^2 (previously treated patients)		
Complete	1 (10%)	0
Major	2 (20%)	15 (10–20)
Minor	0	–
Failure	7 (70%)	69 (21–77)
Total	10	45 (0–77)

Complete, 0 emetic episodes; Major, 1–2 emetic episodes; Minor, 3–5 emetic episodes; Failure, >5 emetic episodes

Adverse events

GR38032F was well tolerated: on direct questioning, mild to moderate sedation was noted in five patients; headaches, reported in four patients, either resolved spontaneously or were successfully treated with 800 mg paracetamol; diarrhea occurred in four patients; transient elevations in AST and/or ALT occurred in three patients but were not associated with any clinical signs or symptoms. These events were considered to be possibly related to GR38032F treatment.

In two patients, thrombocytopenia was observed at the 1-week assessment, but the platelet count returned to within the normal range before the next course of chemotherapy. Thrombocytopenia was also observed in one patient at 24 h posttreatment but resolved at 1 week after treatment. These changes were not considered likely to be due to GR38032F. One patient experienced palpitations of moderate severity accompanied by throbbing, sweating, and

arterial hypertension 22 h after starting the GR38032F infusion. This event was not considered to be related to GR38032F treatment. No extrapyramidal reactions were observed.

Discussion

The results of this pilot study demonstrate that GR38032F is an effective antiemetic agent. As patients receiving high-dose cisplatin experience a minimum of 5 emetic episodes without antiemetic treatment [5, 7], it may be concluded that GR38032F given at a dose of 32 mg (8 mg i.v. loading + 1 mg/h for 24 h) has significant activity against acute cisplatin-induced emesis. Overall, complete or major control of vomiting was achieved in 69% of the patients, with a corresponding effect on nausea.

However, vomiting is known to be easier to prevent in patients receiving lower doses of cisplatin [7, 8, 14], and previous treatment with cisplatin may also affect the degree of nausea and vomiting. A retrospective stratification was therefore carried out, based on the respective dose of cisplatin as well as whether patients were receiving their first or subsequent courses of cisplatin.

At the dose selected, GR38032F seemed to be most effective in naive or previously treated patients receiving cisplatin at doses of 70–99 mg/m^2, with complete and major control achieved in 94% of patients. None of the patients treated with cisplatin within this dose range had possibly alcohol-related carcinomas; thus, the efficacy of GR38032F cannot be attributed to this factor [4]. In this same group of patients, study numbers were too small (seven women, nine men) to enable a conclusion to be drawn as to the effect of differences in sex on efficacy.

GR38032F appeared to be less effective in patients receiving cisplatin at doses of 100–120 mg/m^2 (all previously treated), as it failed to control emesis in 7 of 10 patients. However, all 7 patients who were considered to be failures in this study had experienced a minimum of 10 vomiting episodes over 24 h (range, 10–40) with their previous course of cisplatin, despite the use of an antiemetic regimen that included metoclopramide, methylprednisolone, and diphenhydramine. Younger patients are also known to be more likely to experience a greater degree of emesis associated with chemotherapy [14]. The lower median age of these 7 patients (28 years; range, 18–53 years), compared with that for the study population as a whole (54 years; range, 18–66), suggests that they may have been more prone to refractory emesis. Interestingly, six of these seven patients stated a preference to receive GR38032F with future courses of cisplatin, despite being classified as failures in this study.

In summary, GR38032F was well tolerated, with no serious adverse events. The lack of any extrapyramidal reactions confirms the absence of any dopamine antagonist activity. The encouraging antiemetic activity observed in this open study should be confirmed in comparative studies.

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