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Clinical paper

Use of granisetron in patients refractory to previous treatment with antiemetics

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A multicenter, open-label, compassionate-use trial studied the antiemetic efficacy and tolerability of granisetron in patients who had failed other antiemetic therapies in previous cycles of cytostatic chemotherapy. The antiemetics that had been used previously included metoclopramide, dexamethasone and ondansetron. A total of 517 patients, 456 of whom had failed other antiemetics, were treated in up to 15 successive cycles of chemotherapy. The numbers of patients treated in the first six of these cycles were large enough to allow the drawing of meaningful conclusions from the results. During that period, a complete response was achieved in 53–60% of patients. In addition, antiemetic efficacy was sustained throughout these six repeated treatment cycles. Granisetron was less effective against high-dose cisplatin chemotherapy than against other cytostatic regimens. The treatment was well tolerated—the main adverse events reported were headache and constipation; no serious adverse events were considered to be attributable to the drug. It is concluded that granisetron treatment was effective and well tolerated in patients who had previously failed other antiemetic therapies, including treatment with 5-hydroxytryptamine$_3$ antagonists. [© 1998 Lippincot-Raven Publishers.]

Key words: Antiemetic, granisetron, refractory, repeat-cycle.

Introduction

Nausea and vomiting represent major problems for patients receiving cytostatic chemotherapy. Gastrointestinal symptoms compromise patients' compliance with potentially life-saving therapies[1] but, in addition, incomplete control of nausea and vomiting in the hours immediately after the onset of chemotherapy is also more likely to result in delayed symptoms of nausea and vomiting, and/or anticipatory symptoms in subsequent treatment cycles.[2,3]

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist that has been shown to be an effective antiemetic agent in patients receiving cytotoxic chemotherapy.[4] This drug has provided at least equivalent antiemetic protection to conventional antiemetics,[4,5] and to the other 5-HT$_3$ antagonists, ondansetron and tropisetron.[7,8] Moreover, in the latter cross-over studies, most patients who expressed a preference favored granisetron over ondansetron.[7,8]

Few studies have reported on the effects of antiemetics during repeated cycles of chemotherapy. Those studies that have done, have often noted a decline in antiemetic effect during successive treatment cycles when standard antiemetic regimens are used,[9,10] though other studies have shown a sustained antiemetic effect.[11] In the study reported here, granisetron was used on an open-label, compassionate-use basis over repeated cycles of chemotherapy. Furthermore, most of the patients enrolled had failed on other antiemetic treatments, and therefore were at a high risk for nausea and vomiting. Assessments of the efficacy and tolerability of the drug were made during successive treatments, up to a maximum of 15 cycles.

Materials and methods

Patients

Patients were above the legal age of consent and had given informed consent to their participation in the

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study. The majority of patients had failed antiemetic therapy during the previous cycle of cytostatic treatment because of either a lack of efficacy or adverse events. Patients were excluded from the study if they had received granisetron on any previous occasions; had not undergone cytostatic therapy before; had taken any investigational new drug within the past 3 months or were due to receive one during the next cycle of chemotherapy; or were suffering from serious renal or hepatic dysfunction; or were unable or unwilling to comply with the study protocol.

The study was performed in accordance with the declaration of Helsinki and the protocol was approved by local ethics committees in the trial centers.

Drug administration

Granisetron, 3 mg, was administered i.v. in 0.9% sterile saline (i.v., 20 ml) over a 5 min period that ended 5 min before the start of cytostatic chemotherapy.[12] If satisfactory control of nausea and/or vomiting was not achieved with the initial dose of granisetron, up to two further doses of 3 mg could be administered in the same way, with a minimum period of 10 min between these doses. If control of nausea and vomiting was not achieved using 9 mg of granisetron, rescue medication with standard antiemetics was administered and the patient withdrawn from the study.

During the first treatment cycle, 184 patients received cisplatin as a main agent; the remaining patients received less emetogenic chemotherapy. A maximum of 15 treatment cycles were completed, though most patients completed fewer treatment cycles because of the scheduled termination of their chemotherapy.

Clinical evaluation

The primary end-point was complete response, defined as no vomiting, mild or absent nausea, no requirement for rescue therapy during the first 24 h after the start of chemotherapy and no patient withdrawal from the study. All patients were observed for a minimum of 2 h from the onset of cytostatic chemotherapy. They then received a diary card on which to record, for a period of 24 h after the start of chemotherapy, the worst severity of nausea, the number of episodes of vomiting and the need for either additional doses of granisetron or rescue medication. In addition, adverse events were recorded by asking the patient the non-leading question: 'Do you feel any different in any way since starting the treatment or since the last visit?'. If patients had been discharged within 24 h of the start of chemotherapy, information on efficacy and adverse events was obtained at their next visit, 3–28 days later.

As the trial was open-label and uncontrolled, no formal statistical analyses were performed. The measures of efficacy and adverse events were subjected to descriptive analysis.

Results

Patient characteristics

A total of 517 patients were recruited from 45 centers in Belgium, Canada, France, Germany, The Netherlands, Switzerland and the UK. Of these patients, 161 (31.1%) were male and 355 (68.7%) were female, with data for one patient missing. The mean age of the population was 49 years (range 10–79 years). The majority of the patients (88.2%) were enrolled in the trial having failed previous antiemetic medications

Table 1. Antiemetic therapies that had been used in previous cycles of chemotherapy

Antiemetic agent	Reason for discontinuation of treatment					
	Lack of efficacy	Side-effects	Lack of efficacy and side-effects	Not clinically related	Not stated	Total
Metoclopramide	170	15	15	0	0	200
Dexamethasone	109	10	7	0	0	126
Alizapride	119	3	1	0	0	123
Ondansetron	85	0	2	7	0	94
Chlorpromazine	76	2	1	0	0	79
Others	117	10	15	0	7	149

(Table 1). A total of 61 patients (11.8%) of patients had not received prior chemotherapy but were included in the study and remained in the analysis.

Efficacy

A complete response to treatment was achieved in 53-60% of patients in cycles 1-6 (Figure 1). The proportion of patients showing a complete response remained constant throughout successive treatment cycles. There was no major difference between the patients naive to chemotherapy and those that were not (Table 2). As the number of patients receiving treatment had fallen to 48 by the sixth cycle, data from the later cycles were not included in the analysis.

Patients receiving cisplatin (above 50 mg/m^2) showed fewer complete responses (25.0-57.1%) compared with those receiving other cytostatic agents (59.3-67.9%; Figure 2), with greater incidence of both nausea and vomiting. The numbers of patients receiving cisplatin in cycles 4-6 were too small to allow conclusions to be drawn from the data, but vomiting was a greater problem among patients receiving cisplatin than in patients receiving other agents, by a magnitude of approximately 20% (Figure 3). Likewise, the incidence of nausea was higher and

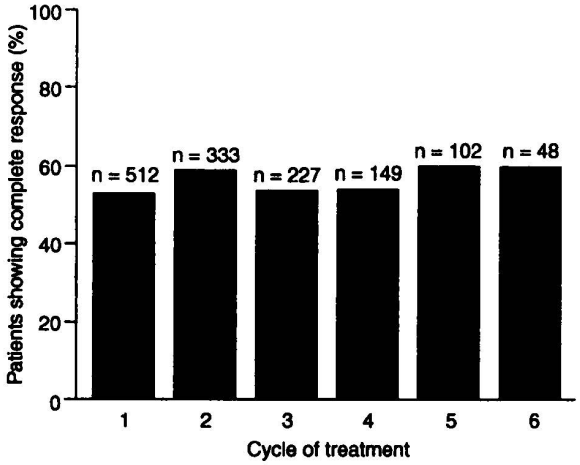

Figure 1. The percentages of patients in whom a complete response to granisetron treatment was achieved (no vomiting and at worst only mild nausea) during six successive cycles of cytostatic chemotherapy. (The numbers given are the total numbers of patients included in each treatment cycle).

Table 2. The number of patients (%) showing a complete response to granisetron in each chemotherapy cycle

Cycle[a]	Number of patients (%)		
	Naive to chemotherapy	Not naive to chemotherapy	All patients
1	64	52	53
2	71	57	59
3	60	53	54
4	60	54	54
5	63	59	60
6	67	60	60

[a]Granisetron given at each cycle.

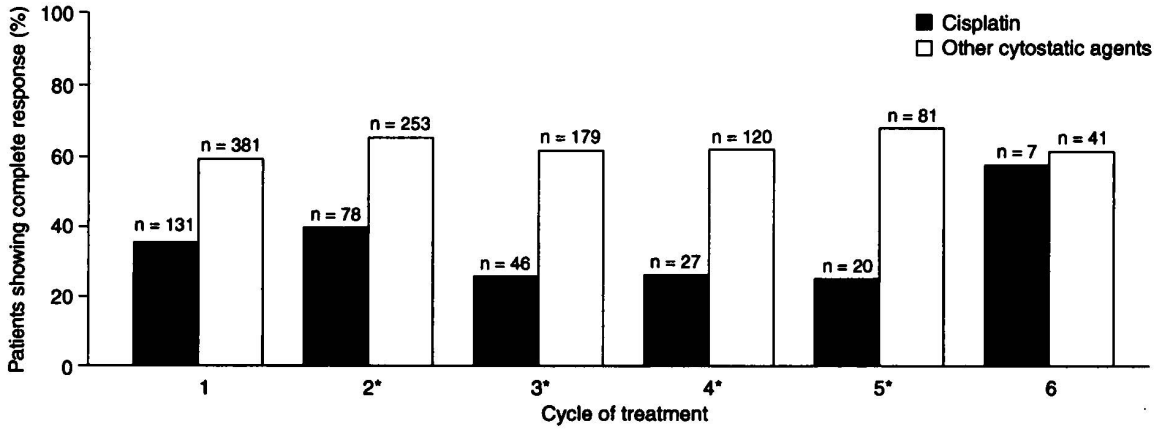

Figure 2. The percentages of patients in whom a complete response to granisetron treatment was achieved during six successive cycles of chemotherapy with either cisplatin (above 50 mg/m^2) or other cytostatic agents. *Patients who did not receive chemotherapy on day 0 of cycle 1 are excluded (two individuals for cycles 2–4 and one individual for cycle 5).

the severity of nausea tended to be worse in the group receiving cisplatin therapy than in other patients. Nevertheless, there appeared to be no further loss of antiemetic efficacy of granisetron treatment in either subgroup across successive cycles of therapy (Figures 2 and 3).

Data for subgroups of patients who had previously received (and failed) different antiemetic therapies showed that granisetron was effective in all of these subgroups. Complete response rates in cycle 1 ranged from 38% (previous treatment with ondansetron) to 72% (alizapride; Table 3).

When the data were grouped according to gender, it could be seen that more male patients showed a complete response than female patients (53.7-100% and 38.5-75%, respectively). There were no differences with respect to age (below 65 or 65 and above).

Overall, 20 and 12% of patients required second and third doses of granisetron, respectively, and approximately 10% received conventional antiemetics as rescue medication.

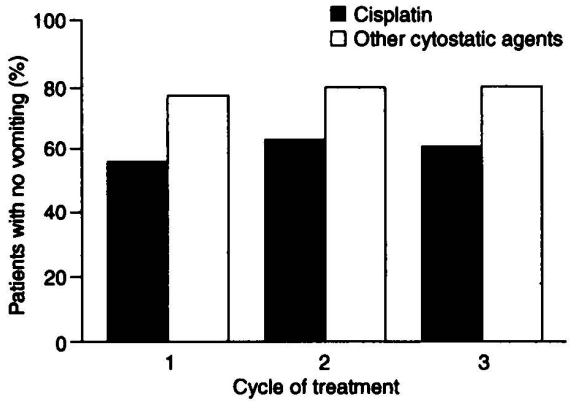

Figure 3. The percentages of patients who showed no vomiting during three successive cycles of chemotherapy with either cisplatin (above 50 mg/m^2) or other cytostatic agents.

Safety

The incidence of adverse events tended to decrease throughout successive cycles of granisetron treatment (Table 4). Only two adverse events were reported by more than 5% of patients in any cycle of treatment: headache (2.0-8.3% of patients) and constipation (2.1-5.3% of patients).

Six patients were reported to have experienced serious adverse events, but none of these were considered attributable to the study medication. Seven patients were withdrawn from the trial because of adverse events. Only one of these—transient memory impairment and somnolence—was considered related to the study medication. All other patients were withdrawn as a result of termination of chemotherapy.

Discussion

The results of this open, uncontrolled trial are of interest because it is one of the first studies to investigate the efficacy of granisetron in patients at a high risk of emesis because they had previously failed other antiemetics.[2,3] The relatively high proportion of patients in this study who required rescue medication

Table 3. The percentages of patients in whom a complete response to granisetron was achieved, grouped with respect to antiemetics previously used

Antiemetics previously used	Cycle of treatment		
	1	2	3
Metoclopramide	47 (92)	43 (54)	37 (34)
Dexamethasone	44 (54)	44 (33)	38 (20)
Alizapride	72 (88)	84 (74)	76 (45)
Ondansetron	38 (35)	45 (23)	58 (18)
Chlorpromazine	71 (56)	88 (51)	84 (32)

The numbers given are the percentage and, in brackets, the total number of patients in that subgroup.

Table 4. Patients who reported adverse events during the first six treatment cycles

	Cycle of treatment					
	1	2	3	4	5	6
No. of patients treated	516	333	227	149	102	48
Patients reporting one adverse event (%)	15.7	14.1	18.9	10.1	13.7	12.5
Patients reporting a severe adverse event (%)	2.9	3.3	3.1	1.3	1.0	4.2
Patients reporting headache (%)	4.3	3.9	4.9	2.0	2.9	8.3
Patients reporting constipation (%)	4.5	3.9	5.3	3.4	2.9	2.1

with conventional antiemetics (10%) probably reflects the high-risk nature of this patient group. In spite of this, the antiemetic efficacy of granisetron recorded in this study (53-60% complete responses over six treatment cycles) was as good as that reported in previous trials involving chemotherapy-naive patients.[4-6,13,14] Moreover, the data suggest that the antiemetic efficacy of granisetron was maintained over repeated cycles of treatment. This result has been reported previously for granisetron (manuscript in preparation)[11,15] and is in contrast to results reported for conventional antiemetics, which appear to lose efficacy over repeated treatment cycles.[9,10] This maintenance of the efficacy of granisetron is unlikely to represent a selection effect, in which patients who showed a good response to treatment remained in the study for longer, because no patients were withdrawn from treatment as a result of a poor response—most withdrew only at the end of their scheduled chemotherapy.

In this study, granisetron provided protection from emesis regardless of the nature of the previous antiemetic medication. Thus, as described previously in a cross-over trial of ondansetron and granisetron,[8] even patients who had proved refractory to treatment with one 5-HT_3 antagonist could gain benefit from the use of another.

Granisetron was well tolerated through successive cycles of therapy. As in other studies with granisetron, few drug-related side-effects were reported, and the most common of these were headache and constipation. This contrasts with the sometimes severe and distressing extrapyramidal side-effects that can be produced by conventional antiemetics, which have dopamine D_2-receptor antagonistic effects.

Conclusions

Granisetron was shown to produce good, reliable antiemetic efficacy in patients who had previously failed on other antiemetic treatments, including another 5-HT_3 antagonist. The effects were maintained throughout several treatment cycles. Granisetron therapy was well tolerated during repeated treatment, with mild headache and constipation the commonest problems.

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