In conclusion, these two studies provide evidence that granisetron (40 μg/kg or 3 mg) achieves a consistently high level of efficacy over repeated cycles of cytotoxic chemotherapy for the majority of patients. However, the exact level of efficacy is difficult to determine, as inevitably some degree of patient selection bias will occur at later cycles as a result of patient withdrawals. Consistent with findings reported for other antiemetics, there is some fall-off in efficacy over multiple cycles of high-dose cisplatin. Controlled, comparative studies in a well defined homogenous patient population are required to estimate more precisely the efficacy of granisetron over multiple chemotherapy cycles, and to allow comparisons to be made between granisetron and other therapies. The present studies demonstrate that granisetron doses of 40 μg/kg and 3 mg are equally effective and well tolerated and confirm that a single 3 mg dose may be recommended for all patients. This is a simple and convenient regimen for effective control of emesis over repeated cycles of chemotherapy.

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Eur J Cancer, Vol. 28A, Suppl. 1, pp. S21-S28, 1992
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

Fractionated Chemotherapy - Granisetron or Conventional Antiemetics?

Volker Diehl
on behalf of the Granisetron Study Group

Two randomised single-blind comparative studies were carried out in patients receiving 5-day fractionated chemotherapy. The first which has been reported previously [1] compared granisetron (40 μg/kg) (n = 103) with alizapride (12 mg/kg) plus dexamethasone (8 mg) (n = 94) while the second compared granisetron (40 μg/kg) (n = 143) with metoclopramide (7 mg/kg) plus dexamethasone (12 mg) (n = 141). Granisetron, unlike alizapride or metoclopramide is a specific 5-HT_3 antagonist. The percentage of complete responders (patients with no vomiting and no worse than mild nausea) over the 5-day treatment period was higher for granisetron than for alizapride/dexamethasone (54% vs. 42.7%) (P = 0.121) or for metoclopramide/dexamethasone (46.8% vs. 43.9%). The percentage of complete responders in the first 24 h was significantly higher for granisetron (90.3%) than for alizapride/dexamethasone (65.9%) (P < 0.001) or for metoclopramide/dexamethasone (87.4% vs. 67.9% P < 0.0001). Granisetron was also superior to both comparators in terms of the time to the first episode of moderate/severe nausea and to less than a complete response. Significantly fewer granisetron patients were withdrawn than in the alizapride/dexamethasone group (P = 0.017) or the metoclopramide/dexamethasone group (P < 0.0001). In both studies more comparator patients were withdrawn due to lack of efficacy and adverse events. Significantly fewer granisetron patients experienced adverse events than in either the alizapride/dexamethasone group (47.6% vs. 61.7%, P = 0.047) or the metoclopramide/dexamethasone group (60.8% vs. 77.3% P = 0.003). Granisetron patients experienced a significantly higher occurrence of constipation in both studies (10.7% vs. 3.2% and 12.6% vs. 2.8%). Headache and fever were also more frequent in the granisetron group, while extrapyramidal effects, reported by 5.3% of the alizapride/dexamethasone group and 20.6% of the metoclopramide/dexamethasone group, were not reported in any granisetron patients.
Eur J Cancer Vol. 28A, Suppl.1, pp. S21-S28, 1992.

INTRODUCTION

THE USE of cytotoxic drugs to treat patients with malignant disease can cause a number of undesirable side effects, both physical and non-physical. In terms of patient perception of the relative importance of these side effects, nausea and vomiting were rated as being the most severe [2]. This chemotherapy-induced nausea and vomiting may be so severe that patients refuse further cycles of chemotherapy. This represents an important clinical problem since, not only does it affect the patients' quality of life during treatment, but it may be lethal if

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the patients refuse potentially curative chemotherapy [3, 4]. There is thus a need for effective antiemetic control in these patients.

One approach to this problem which has been developed for a number of tumour types has been to fractionate the chemotherapy over a number of days. The rationale behind these fractionated regimens is that side effects, such as nausea and vomiting, will be reduced by spreading the cytotoxic insult.

Antiemetic drugs used to reduce these side effects of chemotherapy include the substituted benzamides alizapride and metoclopramide [5]. These two drugs have similar properties [3] acting as dopamine-receptor antagonists at conventional doses. While effective in preventing the mild-to-moderate emesis caused by some cytotoxic drugs, dopamine-receptor antagonists at conventional doses offer little protection against the severe forms of emesis caused by drugs such as cisplatin [6].

Unlike other dopamine-receptor antagonists, metoclopramide, given at high doses, has proved effective against cisplatin-induced emesis [7]. It was recognised that this action of high-dose metoclopramide was mediated via antagonism of 5-HT_3 receptors rather than dopamine receptors [8]. A problem with the use of high doses of dopamine-receptor antagonists has been the occurrence of extrapyramidal side effects [4, 9, 10] particularly in those patients being treated on consecutive days [11].

Granisetron, in contrast with alizapride and metoclopramide, is a selective 5-HT_3-receptor antagonist developed specifically for antiemetic use [8]. It has been shown to be highly effective in combating cisplatin-induced emesis in the ferret [12] while in patients the drug was found to be well tolerated, a single dose of 40 μg/kg being effective in preventing vomiting in cisplatin-treated patients [13].

These studies were set up in order to compare the efficacy and safety of granisetron with that of two commonly used combination regimens, alizapride plus dexamethasone and metoclopramide plus dexamethasone, in patients receiving 5-day fractionated chemotherapy.

PATIENTS AND METHODS

Both studies were multicentre and multinational and were of a single-blind design. Chemotherapy-naive patients, over the legal age of consent, who were scheduled to receive cytostatic therapy for malignant disease, according to one of the following regimens, were eligible for inclusion into both of these studies. The allowed regimens were cisplatin ≥ 15 mg/m²/day or ifosfamide ≥ 1.2 g/m²/day or etoposide ≥ 120 mg/m²/day given on each of 5 consecutive days. Other less emetogenic chemotherapy could be given concomitantly with these primary regimens. Randomisation to receive either granisetron or the comparator antiemetic was carried out centrally (to avoid bias) and stratified according to the primary cytotoxic being administered.

Other inclusion criteria were that patients had given their informed consent to participate in the study and had either a Karnofsky index score of 60% or more (in the study against alizapride/dexamethasone) or a WHO classification score of 2 or less (in the study against metoclopramide/dexamethasone). Patients were excluded from the study if they had marked hepatic dysfunction, renal dysfunction, cardiac failure, active peptic ulcer or gastric compression, a partial or generalised seizure within the last year, a primary or secondary brain tumour or pre-existing acute or chronic nausea and vomiting. Other reasons for exclusion were changes in medication/dosage of central nervous system active drugs and scheduled treatment with corticosteroids, other antiemetics, radiotherapy or any new chemical entity during the study.

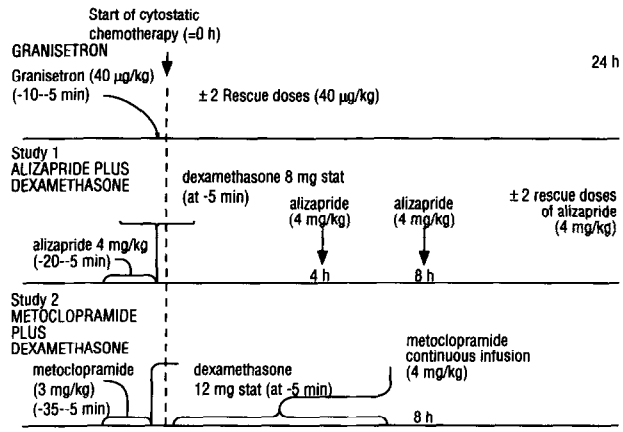

Fig. 1. Daily antiemetic treatment regimens.

Antiemetic dosing regimens

Granisetron was administered prophylactically each day as a 5-min intravenous (i.v.) infusion (40 μg/kg). Two further rescue doses (40 μg/kg) were allowed within each 24-h period if breakthrough nausea or vomiting occurred. The dosing regimen of granisetron and of the two comparator combination regimens is shown in Fig. 1. In the case of the comparator regimens, provision for an alizapride/metoclopramide dose reduction was made in cases where antiemetic efficacy was established but unacceptable side effects (e.g. extrapyramidal syndrome) were seen.

Withdrawals

In cases where adequate control of emesis was not obtained (in any of the treatment groups), the patient was withdrawn from the study and treated with other medication of the physician's own choice.

Assessments

Assessments of nausea and vomiting were made at 6-h intervals throughout the 5-day treatment period and on a daily basis for a further 7 days using diary cards. The primary efficacy criteria was the percentage of complete responders (no vomiting and no worse than mild nausea) over the 5-day treatment period. The efficacy criteria used in these studies are defined in Table 1.

Table 1. Efficacy criteria

Complete Responder	No vomiting and no worse than mild nausea
Major Responder	1 vomit and/or moderate to severe nausea
Minor Responder	2 - 4 vomits
Failure	> 4 vomits

Vomit = Retch.

Table 2. Patient demographics

	STUDY 1		STUDY 2	
	Granisetron	Alizapride/ Dexamethasone	Granisetron	Metoclopramide/ Dexamethasone
No. of patients	103	94	143	141
Males	81	74	114	119
Females	22	20	29	22
Mean age (years)	50.2	48.2	46.7	46.3
Primary cytostatic received:				
Cisplatin	74 (72%)	68 (72%)	128 (90%)	120 (85%)
Ifosfamide	29 (28%)	25 (27%)	15 (10%)	20 (14%)
Etoposide	-	1 (1%)	-	1 (1%)
Mean cytostatic therapy dose:				
Cisplatin (mg/m²)	20.4	19.6	20.0	20.0
Ifosfamide (mg/m²)	1565.2	1619.0	1484.0	1438.0
Etoposide (mg/m²)	0	128.4	0	122.0

Statistical analyses

Prior to any analysis being performed a set of criteria were drawn up to define "treated" and "evaluable" patients, the conditions under which patients would be included into the various analyses and how withdrawals or missing assessments would be evaluated.

"Treated patients" were defined as those who received any antiemetic treatment; "evaluable patients" were those treated patients for whom assessable data were available. Patients were included in the day-by-day analysis if they completed that day, in the 5-day analysis if they completed the 5 days, and in the survival analysis up to the point where no further information was available.

Patients withdrawn due to lack of efficacy or an antiemetic-related adverse event were included as failures at the appropriate time point. Those withdrawn due to deterioration of condition, change of chemotherapy regimen or a non-antiemetic-related adverse event were excluded from the 5-day analysis but were included in the day-by-day and survival analyses up to the point of withdrawal.

Three assumptions were made for missing efficacy assessments. If a single assessment was missing an assumption was made based on the flanking data, the worst case was assumed if this was conflicting. If two or more efficacy assessments were missing it was assumed that there was nausea and vomiting. If the patient was asleep it was assumed that no nausea/vomiting occurred.

For the study against alizapride/dexamethasone, the target sample size was 200 patients, as 100 patients per group were sufficient to detect a difference of 19% between groups (5% significance level: at least 80% power).

For the study against metoclopramide/dexamethasone, the target sample size was 300, as 150 patients per group were sufficient to detect a difference of 16% (5% significance level: at least 80% power).

The statistical techniques used in interpreting the data in this study were the Cox Log Rank test and the chi-squared test. In all cases a two-tailed significance level of 5% was regarded as statistically significant.

Demographics

The studies were carried out in 46 centres in Belgium, France, Germany, Holland, Switzerland and the U.K. In the first study 103 patients received granisetron and 94 received alizapride plus dexamethasone while in the second study 143 patients received granisetron and 141 received metoclopramide plus dexamethasone. Cisplatin was the primary cytostatic received by the majority of patients in all antiemetic treatment groups, ifosfamide was received by most of the others and etoposide by a single comparator patient in each study. Further details of patient demographics and of the numbers of patients receiving each primary cytostatic are given in Table 2.

Less emetogenic chemotherapy was allowed concurrently with the primary cytostatic; it was found that the numbers of patients receiving other cytostatic agents were in general well balanced across the two antiemetic groups in both studies.

RESULTS

Study 1: Granisetron vs. alizapride plus dexamethasone

In the analysis of complete response over 5 days, 3 patients were dropped from the granisetron group and 5 from the comparator group (according to the pre-determined rules for including patients into the analysis). Thus the number of patients analysed were 100 (granisetron) and 89 (comparator).

The number of complete responders over the 5-day treatment

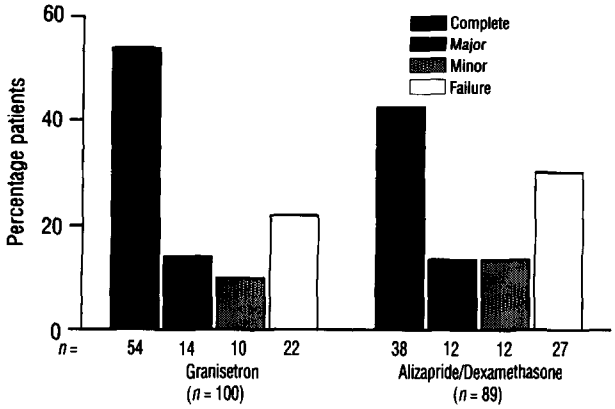

Fig. 2. Responder categories over 5-day treatment period for Study 1: granisetron vs. alizapride plus dexamethasone.

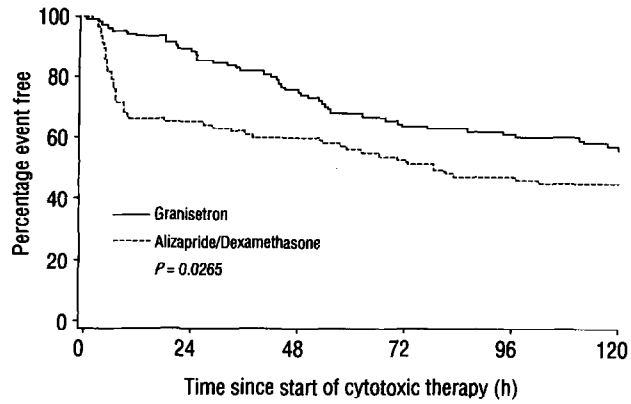

Fig. 3. Survival time to less than a complete response over the 5-day study period for Study 1: granisetron vs. alizapride plus dexamethasone.

period was 54/100 in the granisetron group (54%) and 38/89 in the comparator group (42.7%) ($P = 0.121$). A breakdown of patient response over the 5 days according to responder category is shown in Fig. 2. An analysis of the time to less than a complete response over the 5-day treatment period is shown in Fig. 3. Patients receiving granisetron maintained a complete response for a significantly longer period than those receiving comparator medication ($P = 0.0265$). In addition it was found that there was a significant difference in the survival time to the first episode of moderate or severe nausea in the 12-day study period as patients receiving granisetron did not experience moderate or severe nausea for a significantly longer period than those in the comparator group ($P = 0.0349$).

An analysis of the complete response rate on a day-by-day basis showed a significantly greater number of complete responders in the granisetron group on day 1 (93/103) = (90.3%) than in the alizapride/dexamethasone group (60/91) = (65.9%) ($P < 0.001$). There was no significant difference between the two antiemetics on the subsequent 4 days. It was found that a single 40 μg/kg prophylactic dose of granisetron was the only antiemetic required by the majority (> 85%) of patients (Table 3).

The number of patients withdrawn from the granisetron group ($n = 5$) during the 5-day treatment period was significantly less ($P = 0.017$) than in the comparator group ($n = 14$) (Table 4) and fewer granisetron patients were withdrawn due to lack of efficacy and adverse events.

Significantly fewer granisetron patients suffered adverse events during the study (47.6% vs. 61.7%, $P = 0.047$). The incidence of constipation was significantly greater in the granisetron group (10.7% vs. 3.2%; $P = 0.04$). Extrapyramidal effects, not seen at all in granisetron patients, were reported by 5.3% of alizapride/dexamethasone patients ($P = 0.02$). The other adverse events which were most frequently reported were leucopenia, fever and headache. There was no significant difference in their incidence across the two antiemetic groups (see Table 5.)

Study 2: Granisetron vs. metoclopramide plus dexamethasone

In the analysis of complete response over 5 days, 2 patients were dropped from each antiemetic group according to the predetermined rules for including patients into the analysis. Thus the numbers of patients included into the analysis were 141 for the granisetron group and 139 for the metoclopramide plus dexamethasone group.

The percentage of complete responders over the 5-day treatment period was 46.8% for the granisetron group (66/141) and 43.9% for the comparator group (61/139). A breakdown of the 5-day efficacy results by responder category is shown in Fig. 4. When the profile of complete/major/minor responders and failures was compared for the two antiemetic treatments, there was a significant difference in the overall efficacy profile in favour of granisetron ($P = 0.013$). While granisetron showed a slight numerical superiority in terms of numbers of complete and major responders, the difference in the two groups lies in the greater number of minor responders and fewer failures for granisetron. The survival time to less than a complete response over the 5-day treatment period was longer for the granisetron group, although not significantly so (Fig. 5). The survival time to the first episode of moderate or severe nausea over the 12-day study period was also longer for the granisetron group, again this result was not statistically significant.

An analysis of the complete response rate on a day-by-day basis showed a significantly greater number of complete responders in the granisetron group on day 1 (87.4% vs. 67.9%; $P < 0.0001$). There was no significant difference in the number of complete responders in the two antiemetic groups on the subsequent 4 treatment days.

A single prophylactic dose of granisetron (40 μg/kg) was the only antiemetic required by the majority of patients (Table 3).

The number of patients withdrawn from the granisetron group ($n = 11$) during the 5-day treatment period was significantly less ($P < 0.0001$) than in the metoclopramide/dexamethasone group ($n = 38$) (Table 4). Fewer granisetron patients were withdrawn due to adverse events and lack of efficacy.

A significantly lower percentage of granisetron patients reported adverse experiences during the study (77.3% vs. 60.8%, $P = 0.003$). The incidence of headache, constipation and fever was significantly greater in granisetron patients. Extrapyramidal effects, not seen at all in granisetron patients, were reported in 20.6% of metoclopramide/dexamethasone patients ($P < 0.0001$). The other adverse events which were most frequently reported were diarrhoea, hypertension, abdominal pain and leucopenia. There was no significant

Table 3. The number of patients who received 1, 2 or 3 doses of granisetron (40 μg/kg) during each 24-h period

Study 1: Granisetron vs. Alizapride/Dexamethasone				Study 2: Granisetron vs. Metoclopramide/Dexamethasone			
	No. of doses				No. of doses		
DAY	1	2	3	DAY	1	2	3
1	94%	3%	3%	1	92%	7%	1%
2	93%	5%	2%	2	84%	12%	4%
3	88%	7%	5%	3	84%	12%	4%
4	85%	10%	5%	4	82%	13%	5%
5	87%	7%	6%	5	86%	11%	3%

Table 4. Summary of reasons for patient withdrawals during the 5-day study period

	STUDY 1			STUDY 2:	
Reason:	Granisetron	Alizapride/ Dexamethasone	Reason	Granisetron	Metoclopramide/ Dexamethasone
Lack of efficacy	1	2	Lack of efficacy	4	9
Lack of efficacy & adverse events	1	4	Lack of efficacy & adverse events	0	4
Adverse events	1	3	Adverse events/death	5	17
Adverse events + other	0	2	Adverse events + violation	0	3
Deterioration of condition	1	0	Other*	2	5
Other*	1	3			
	5	14		11	38

Significantly more patients were withdrawn from the alizapride/dexamethasone group ($P = 0.017$) and from the metoclopramide/dexamethasone group ($P = 0.0001$) than for granisetron.

*Adverse events plus concurrent disease and other reasons.

difference in their incidence across the two antiemetic groups (Table 5).

DISCUSSION

While the use of fractionated chemotherapy is generally restricted to a number of specific cancer types (e.g. teratoma, lung cancer) it nevertheless forms a relatively large percentage of all chemotherapy administered in certain countries. Thus the effective control of emesis in fractionated chemotherapy regimens would be of benefit to a relatively large number of patients.

The comparators chosen for both studies were commonly used combination antiemetic regimens. In terms of efficacy, all of the results show a common trend towards numerical superiority of granisetron over both comparator regimens. The 5-day complete responder rate for granisetron was at least equivalent to that for metoclopramide/dexamethasone (46.8% vs. 43.9%) and was numerically superior to that for alizapride/dexamethasone (54% vs. 42.7%). The 5-day response profile (complete/major/minor/failure) was significantly better for granisetron than for metoclopramide/dexamethasone ($P = 0.013$). In addition, granisetron was superior to both comparators in terms of survival time to less than a complete response over the 5-day treatment period and in terms of survival time to first episode of moderate/severe nausea. These differences in survival times were both statistically significant for the study against alizapride/dexamethasone.

These results are not unexpected in view of the known mechanism of action of these antiemetics. Both alizapride and metoclopramide (at conventional doses) act via dopamine-receptor antagonism [14]. Dopamine-receptor antagonists offer little protection against the more severe forms of emesis evoked by drugs such as cisplatin [6]. Unlike other dopamine-receptor antagonists, metoclopramide at high intravenous doses was found to reduce cisplatin-evoked emesis [6]. This suggested that this antiemetic activity of high-dose metoclopramide was not mediated by dopamine-receptor antagonism [6]. It was subsequently suggested that it may have been mediated by 5-HT_3 receptor antagonism [8].

Alizapride is a newer drug than metoclopramide, but has a similar structure and properties [3]. Some studies indicated that it had superior antiemetic efficacy to metoclopramide [3, 15], while others contradicted this [3, 14, 16]. These latter findings may indicate that alizapride (at high dose) does not possess 5-HT_3 receptor antagonist properties.

Granisetron, in contrast with the comparator antiemetics, is a selective 5-HT_3 receptor antagonist which was developed specifically for antiemetic use [8]. It would therefore be

Table 5. The incidence of adverse events during the studies

	STUDY 1			STUDY 2		
	Granisetron	Alizapride/ Dexamethasone		Granisetron	Metoclopramide/ Dexamethasone	
Total number of patients	103 (100%)	94 (100%)		143 (100%)	141 (100%)	
Number with adverse events	49 (47.6%)	58 (61.7%)	$P = 0.047$	87 (60.8%)	109 (77.3%)	$P = 0.003$
Leucopenia	12 (11.7%)	15 (16.0%)	NS	9 (6.3%)	13 (9.2%)	NS
Constipation	11 (10.7%)	3 (3.2%)	$P = 0.041$	18 (12.6%)	4 (2.8%)	$P = 0.002$
Hypertension	1 (1.0%)	1 (1.1%)	NS	17 (11.9%)	21 (14.9%)	NS
Fever	8 (7.8%)	4 (4.3%)	NS	14 (9.8%)	2 (1.4%)	$P = 0.002$
Headache	7 (6.8%)	2 (2.1%)	NS	21 (14.7)	6 (4.3%)	$P = 0.003$
Diarrhoea	3 (2.9%)	3 (3.2%)	NS	12 (8.4%)	16 (11.3%)	NS
Extrapyramidal effects	0 (0%)	5 (5.3%)	$P = 0.02$	0 (0%)	29 (20.6%)	$P < 0.0001$
Abdominal pain	0 (0%)	1 (1.1%)	NS	11(7.7%)	10 (7.1%)	NS

NOTE: All adverse events which occurred in more than 5% of patients in either study were included in this table.

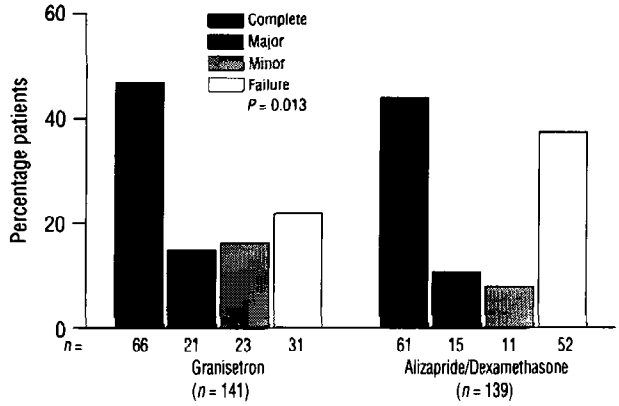

Fig 4. Responder categories over 5-day treatment period for study 2: granisetron vs. metoclopramide plus dexamethasone.

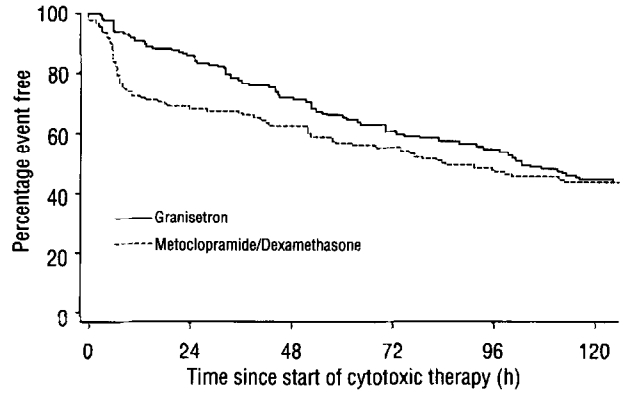

Fig. 5. Survival time to less than a complete response over the 5-day study period for study 2: granisetron vs. metoclopramide plus dexamethasone.

expected to be more effective than either comparator against the more severe emesis evoked by drugs such as cisplatin. This is, in fact what the results of these studies showed. Granisetron was marginally superior to the metoclopramide regimen and more markedly superior to the alizapride regimen in 5-day efficacy.

It was noted by Triozzi and Laszlo [9] that with repeated daily administration of chemotherapy for as long as 5 days, the pattern of nausea and vomiting may be such that the occurrence of these events peaks during the first day. It is thus particularly significant that the efficacy results for granisetron on day 1 were superior to those of either comparator. On the first study 90.3% of granisetron patients were complete responders on day 1 compared to 65.9% of alizapride/dexamethasone patients ($P < 0.001$) while in the second study the corresponding figures were 87.4% for granisetron and 67.9% for metoclopramide/dexamethasone ($P < 0.0001$). These results show a possible advantage in using granisetron since it maintains complete control of emesis in up to approximately 90% of patients on day 1, the most likely time for emesis to occur in patients receiving fractionated chemotherapy. From the survival analyses to less than complete response this significant fall-off in efficacy on day 1 for the comparator groups can be clearly seen. In both cases the major fall-off occurs within the first 12 h. In contrast, there was no sharp fall-off in efficacy in the granisetron group either during day 1 or during the entire study period (days 1-5). The longer survival time to less than a complete response and to the first episode of moderate or severe nausea is another clear advantage of using granisetron, seen in the context of this information.

In Fig. 1 the daily antiemetic treatment regimens for each of the study groups is represented schematically. Both of the comparator regimens are complicated; alizapride/dexamethasone involves multiple infusions of antiemetic while metoclopramide/dexamethasone requires an 8-h continuous infusion following chemotherapy. In addition, both comparator antiemetic regimens allowed for a dose reduction (of the alizapride/metoclopramide) in patients who had good emetic control but experienced unacceptable side effects. This was required by a relatively small number of those patients receiving alizapride (5/94), but by a much greater number of

metoclopramide patients (47/141). These dose reductions represent a further inconvenience of these comparator treatment regimens. Granisetron, in contrast, offered the convenience of a single prophylactic dose, as can be seen from Table 3; this was the only antiemetic treatment required by the majority of patients (> 82%). Of those patients who did require further granisetron rescue doses, they generally responded well and their symptoms resolved.

The number of patients withdrawn during the 5-day treatment period was significantly greater, both for alizapride/dexamethasone ($P = 0.017$) and for metoclopramide/dexamethasone ($P < 0.0001$) than for granisetron (Table 4). More comparator patients were withdrawn due to lack of efficacy and adverse events, this is not unexpected in view of the superior efficacy seen with granisetron.

The percentage of patients who reported adverse events was significantly less for granisetron than for either comparator (see Table 5). A number of the most frequently reported adverse events occurred more frequently in the granisetron group than in the comparator group. These events were constipation, headache and fever. Constipation, reported in significantly more of the granisetron patients in both studies, is a recognised side effect of 5-HT_3 receptor antagonists [17, 18], granisetron is known to slow large bowel transit time [17]. Headache is also a recognised side effect of granisetron, the 14.7% incidence reported in the study against metoclopramide/dexamethasone is typical of the incidence reported in previous 1-day studies of granisetron [13]. The lower incidence of headache (which occurred in 6.8% of patients over the 5 days) noted in the study against alizapride/dexamethasone is an encouraging result, suggesting that repeated treatment does not increase the incidence of this event. The severity of headaches were generally mild and they either resolved spontaneously or responded well to analgesics such as paracetamol.

The other adverse event which occurred more frequently in the granisetron group was fever. Fever is a common occurrence in cancer patients, it may be caused by a number of factors. It is possible that the difference in the incidence of fever between granisetron and the comparator groups is caused by dexamethasone which only the comparator groups received. It is known that steroids (such as dexamethasone) can mask a febrile response [19], this could have resulted in a lower incidence of fever being reported in the comparator groups.

Of the other frequently reported adverse events, leucopenia and diarrhoea are recognised side effects of chemotherapy [2, 20]. Their incidence was not significantly different between the granisetron and comparator treatment groups. The reported incidence of leucopenia in these studies may be an underestimate because its worse incidence (at 5-10 days for ifosfamide and 18-23 days for cisplatin [21]) may not have corresponded with the days on which laboratory tests were carried out. The incidence of abdominal pain and of hypertension was relatively high in both antiemetic groups in the granisetron vs. metoclopramide/ dexamethasone study. However, there were no significant differences between treatment groups.

Extrapyramidal effects were not seen in any of the granisetron patients but significantly, occurred in 5.3% of alizapride/dexamethasone patients ($P = 0.02$) and 20.6% of metoclopramide/dexamethasone patients ($P < 0.0001$). This result was not unexpected since extrapyramidal reactions have been noted to be a major side effect of the use of dopamine-receptor antagonists [8], particularly in those patients receiving consecutive days treatment [11] as is the case here. The association of high-dose metoclopramide in particular with extrapyramidal effects has been documented [4, 9]. Granisetron, a specific 5-HT_3 antagonist [22] has not been noted to cause extrapyramidal effects in any studies to date [13, 23-25].

In conclusion, granisetron is significantly better than alizapride/dexamethasone and at least equivalent to metoclopramide/dexamethasone in controlling nausea and vomiting in patients receiving 5-day fractionated chemotherapy. It also offers a much more convenient dosing regimen and causes significantly fewer adverse events.

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Eur J Cancer, Vol. 28A, Suppl. 1, pp. S28-S32, 1992
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

Oral Granisetron - Simple and Effective: A Preliminary Report

Anne Hacking
on behalf of the Granisetron Study Group

This randomised, double-blind, study was carried out in 930 patients in order to examine the efficacy and safety of oral granisetron in the dose range 0.25, 0.5, 1.0 and 2.0 mg twice daily. Oral granisetron was administered for either 7 or 14 days according to the chemotherapy regimen used. A total of 930 patients were enrolled into this study in order to be able to detect a difference of 15% between groups (80% power). The preliminary results showed that at 7 days efficacy was significantly greater for 1.0 mg b.d. (58.5%) than for 0.25 mg b.d. (43.7%) and indicated that, of the doses examined, the 1.0 mg b.d. dose was optimal in patients receiving moderately emetogenic chemotherapy. In agreement with this there were more withdrawals from the 0.25 and 0.5 mg groups due to lack of efficacy. The adverse events most frequently reported (in > 5% of patients) were constipation, headache, abdominal pain, fever, leucopenia and asthenia. The latter three are recognised side effects of the primary disease and of chemotherapy. The incidence of headache was similar to that seen in previous granisetron studies. Abdominal pain may have been related to constipation. The incidence of constipation (25.9%) was higher than that reported in previous granisetron studies but was not dose related. Thus oral granisetron at 1.0 mg twice daily is an effective antiemetic, offering a convenient dosing regimen without significant adverse events.
Eur J Cancer, Vol. 28A, Suppl. 1, pp. S28-S32, 1992.

INTRODUCTION

PATIENTS receiving chemotherapy for malignant disease have noted the most severe side effects of this treatment as being vomiting and nausea [1]. These side effects have a number of important implications, both for the patients' quality of life and because of further medical complications such as dehydration, electrolyte imbalance, malnutrition, vitamin deficiencies and oesophageal tears [2]. However, the most important consequence of severe nausea and vomiting is that patients may refuse further potentially curative chemotherapy [2], in which case these side effects assume a potentially lethal toxicity [3].

A variety of antiemetic drugs have been used to treat chemotherapy-induced emesis, these include dopamine-receptor antagonists, synthetic cannabinoid derivatives and other drugs which facilitate their antiemetic action (e.g. dexamethasone, lorazepam) [4]. While dopamine-receptor antagonists are effective against the mild-to-moderate emesis evoked by some cytotoxics, they offer little protection against the more severe emesis evoked by drugs such as high-dose cisplatin [4]. Metoclopramide is an exception to this, as it is effective, at high doses, against cisplatin-induced emesis. This action is mediated by antagonism of 5-HT_3 receptors rather than dopamine-receptor antagonism [5]. The problem of using high doses of metoclopramide are the serious extrapyramidal side effects associated with its use [2, 6, 7].

Recognition that high-dose metoclopramide mediated its antiemetic effects via 5-HT_3 receptor antagonism led to the identification of the serotonin-3 receptor antagonists as a new class of antiemetic agents [8]. Granisetron is a specific [9] and extremely potent [8] 5-HT_3 receptor antagonist which has been developed as an intravenous (i.v.) drug and is currently under development as an oral formulation.

Three pilot studies have already been performed in order to determine the antiemetic efficacy of various oral doses of

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