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Does Granisetron Remain Effective Over Multiple Cycles?

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on behalf of the Granisetron Study Group

Intravenous (i.v.) granisetron was made available to patients who had received the drug during their first course of chemotherapy and requested granisetron prophylaxis at subsequent cycles. Initially at each further cycle patients received 40 μg/kg in each further cycle; this was later simplified to 3 mg. 574 patients were treated with 40 μg/kg over 1966 cycles of emetogenic chemotherapy in study 1. 335 patients (81 of whom transferred from study 1) received 3 mg over 785 cycles in study 2. With either regimen about 60% of all patients gained complete protection of symptoms over the 24-h postchemotherapy for up to 8 cycles. Complete response was maintained at around 70% in the subgroup of patients treated with moderately emetogenic regimens. Efficacy decreased over 5 cycles of cisplatin (≥ 50 mg/m²) from approximately 59% at the first additional cycle to around 37% at the fifth. This could, in part, be explained by a reversal in the proportions of males (low risk) to females (high risk) during the study. Withdrawal was largely due to completion of chemotherapy courses; approximately 15% of patients discontinued treatment for reasons possibly related to poor emetic control and 10% for unspecified reasons. Granisetron was well tolerated and no new toxicity developed following repeated exposure. In conclusion, granisetron maintained its efficacy over repeated cycles in most patients, although some fall-off occured with high-dose cisplatin. 40 μg/kg and 3 mg were equally effective.
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INTRODUCTION

DEVELOPMENT of the new class of antiemetic agents, the 5-HT_3 receptor antagonists, represents an important advance in the management of cytotoxic-induced emesis. Granisetron, a potent and selective 5-HT_3 antagonist, prevents nausea and vomiting in approximately 60% of patients receiving high-dose cisplatin [1] and as many as 75% of patients treated with other emetogenic agents [2]. Furthermore, effective emetic control can be gained without risk of extrapyramidal reactions, the major drawback to regimens containing high-dose metoclopramide.

Complete relief of nausea and vomiting is now possible for many patients receiving their first cycle of emetogenic chemotherapy, but it is uncertain whether this level of efficacy is maintained over subsequent cycles of chemotherapy.

Although the literature is limited, two recent studies have shown that the efficacy of conventional antiemetics decreases over successive cycles [3, 4]. Following prophylaxis with high-dose metoclopramide plus corticosteroid regimens, protection from vomiting, but less so from nausea, has been found to reduce from the first to the third cycle of cisplatin (≥ 50 mg/m²) therapy [3]. Additionally, the efficacy of an intravenous (i.v.) methylprednisolone-containing regimen decreased over 6 consecutive cycles of adjuvant FAC (5-fluorouracil, adriamycin and cyclophosphamide) in breast cancer patients [4].

Two studies were conducted to investigate whether the efficacy of intravenous granisetron at doses of 40 μg/kg and 3 mg (equivalent to 40 μg/kg in a 75 kg person) is maintained over repeated courses of emetogenic chemotherapy. In addition, the issue of whether the safety profile changed over successive cycles was examined.

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PATIENTS AND METHODS

Two open-label studies were carried out in nine countries to allow patients who had participated in granisetron protocols in their first cycle of chemotherapy to receive intravenous granisetron prophylaxis at subsequent cycles if they so wished.

Patients gave their informed consent to participate in these studies and were free to withdraw at any time. Approval was gained from the ethics committees of the participating hospitals and the studies were conducted according to the Declaration of Helsinki (1964, amended 1975, 1983). Patients were eligible if they were over the legal age of consent and were due to receive further cycles of the same chemotherapy regimen containing at least one of the following i.v. cytotoxics: carboplatin ≥ 300 mg/m²; cisplatin ≥ 20 mg/m²; cyclophosphamide ≥ 600 mg/m² (in combination); dacarbazine ≥ 350 mg/m² and <500 mg/m²; doxorubicin ≥ 40 mg/m² (single agent) or ≥ 25 mg/m² (in combination); epirubicin ≥ 75 mg/m² (single agent); epirubicin ≥ 50 mg/m² (in combination); mustine ≥ 6 mg/m².

Patients were excluded if they had marked hepatic or renal dysfunction or severe congestive cardiac failure (New York Heart Association grade III or IV); an active peptic ulcer, gastric compression or tumour involvement of the gastrointestinal tract. Patients who had taken any other research drug within the previous 3 months or due to receive such a drug during the study were also excluded.

Routine administration of other antiemetics during the initial 24-h post-chemotherapy period at each cycle was not allowed except where medically indicated due to failure of study medication. Any patient experiencing a serious adverse event

suspected to be associated with granisetron was not permitted to receive further courses of the study drug.

In study 1, conducted between April 1988 and June 1989, i.v. granisetron was administered at each successive cycle as a 40 μg/kg prophylactic dose infused over 5 min completing 5 min before chemotherapy. Intervention with one or two additional 40 μg/kg i.v. doses, given at least 10 min apart, was permitted within 24 h if adequate symptom control was not gained with the initial dose. From July 1989 onwards (study 2), the dosage regimen was simplified to a fixed 3 mg i.v. prophylactic dose (administered in the same way as described above) plus a further one or two 3 mg doses if required during the initial 24 h. Thus, the maximum total daily doses permitted were 120 μg/kg and 9 mg in studies 1 and 2, respectively.

Nausea severity and vomiting were assessed in hospital for up to 24 h at each cycle. If patients were discharged within 24 h, symptoms occurring post-chemotherapy were recorded at the follow-up consultation 3-28 days later. The time of the first occurrence of nausea and vomiting was noted. If at any stage, the patient experienced severe or persistent nausea or vomiting, uncontrolled by the maximum permitted dose of granisetron, other conventional antiemetics were administered.

Adverse events were recorded during the study day, and at the follow-up consultation. Patients were asked the following non-leading question in order to elicit adverse events: "Do you feel different in any way since starting treatment or since the last assessment?"

Patients continued to receive granisetron according to the study protocols for the duration of their course of chemotherapy. If treatment was discontinued prematurely, the reason for withdrawal was noted.

Data analysis

Formal statistical analysis was not considered appropriate for these open, uncontrolled studies and therefore only descriptive review of data in the form of charts and tables was performed. Data on the complete patient population participating in study 1 were reviewed. Study 2 was on going at the time of cut-off of data collection (May 1991) and an interim review was performed on all data held on the central SmithKline Beecham database at this date. The primary efficacy variable in both studies was the percentage of complete responders within the initial 24 h following the start of chemotherapy. A complete responder was defined as a patient experiencing no vomiting and no worse than mild nausea.

RESULTS

In total, 828 patients were enroled into these two studies and data were collected on 2751 additional courses of granisetron treatment. The characteristics of the patients participating in both studies are presented in Table 1. All patients had previously taken part in a granisetron protocol at their initial cycle of chemotherapy. The patient populations participating in both studies were similar in terms of age and the proportion of males to females. A greater percentage of patients in study 2 were undergoing treatment with high-dose cisplatin regimens compared with study 1 (52.8% vs. 35.7%).

The percentage of complete responders by cycle of chemotherapy is shown in Fig. 1 following granisetron doses of 40 μg/kg or 3 mg. The complete response rate remained steady

Table 1. Patient characteristics

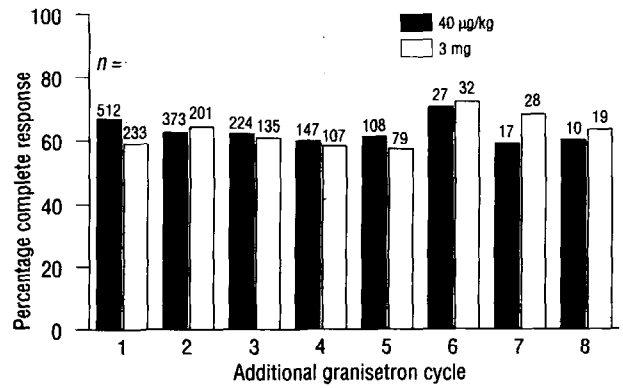
	Granisetron dose	
	Study 1 40 μg/kg	Study 2 3 mg
No. of patients	574	335*
No. of additional cycles	1966	785
Sex-ratio (M:F)	1/1.2	1/1.3
Mean age (years)	53	53
Primary cytotoxic -		
Cisplatin ≥ 50 mg/m²	35.7%	52.8%
Other chemotherapy regimens	64.3%	47.2%

* 81 patients transferred from Study 1 to Study 2

for up to 8 additional cycles, with approximately 60% of patients gaining complete protection at each cycle. The pattern of response was similar following both prophylactic doses of granisetron; a small increase in response rate was noted at additional cycle 6 with both granisetron dosage regimens. Insufficient patients participated in more than 8 additional cycles to allow assessment of efficacy at later cycles.

In order to investigate the influence of the primary cytotoxic regimen on the efficacy of granisetron over repeated cycles, the data were grouped into those patients receiving moderately emetogenic cytotoxics (Fig. 2) and those having courses of high-dose cisplatin (≥ 50 mg/m²) (Fig. 3). With both granisetron regimens, the proportion of complete responders was maintained at approximately 60-70% for up to 8 additional cycles of moderately emetogenic therapy. There was a reduction in the efficacy of granisetron in patients followed for 5 additional cycles of high-dose cisplatin treatment (Fig. 3). In the cisplatin subgroup in study 1, the percentage of complete responders decreased from 59.0% at the first additional cycle to 33.3% at the fifth. The corresponding percentages for study 2 were 56.5% falling to 41.4% after 5 consecutive cycles. A cut-off at 5 additional cycles was taken because the number of patients receiving 6 or more additional cycles was too small to provide meaningful data.

The high-dose cisplatin subgroups from both studies were combined and analysed according to gender (Fig. 4). The percentage of complete responders in males was approximately



[a]5 patients (6 cycles) were not evaluable for anti-emetic efficacy

Fig. 1. Percentage of complete responders[a] over repeated cycles of chemotherapy: comparison of granisetron 40 μg/kg and 3 mg doses.

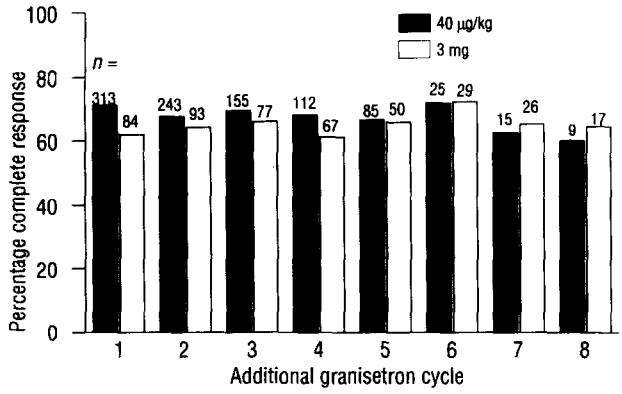


Fig. 2. Percentage of complete responders by cycle of moderately emetogenic chemotherapy: comparison of granisetron 40 μg/kg and 3 mg doses.

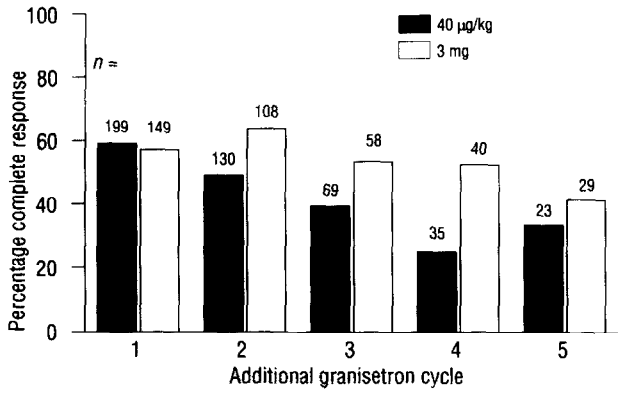
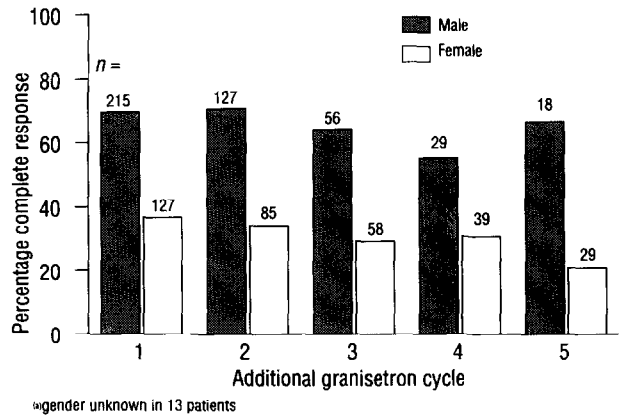
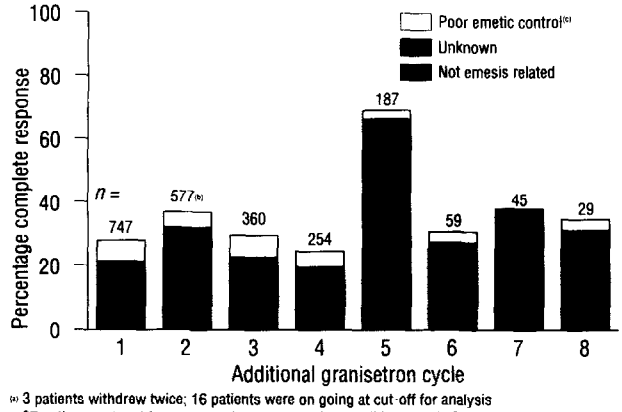


Fig. 3. Percentage of complete responders by cycle of cisplatin (≥ 50 mg/m²) therapy: comparison of granisetron 40 μg/kg and 3 mg doses.



[a]gender unknown in 13 patients

Fig. 4. Percentage of complete responders by cycle of cisplatin (≥ 50 mg/m²): comparison of response according to gender[a].



[a] 3 patients withdrew twice; 16 patients were on going at cut-off for analysis
[b] 37 patients entered from other primary protocols at additional cycle 2
[c] Includes: inadequate antiemetic control; loss to follow up; refusal of therapy; adverse events

Fig. 5. Reasons for withdrawal[a] following each additional cycle of granisetron (40 μg/kg or 3 mg).

double that seen in females at each cycle. In contrast to the marked decrease in efficacy over successive cycles seen in Fig. 3, complete response was almost sustained over 5 cycles in both sexes. Inspection of the demographics of the high-dose cisplatin patients revealed that the proportions of males to females reversed during the course of the study from an initial excess of males (M/F ratio at cycle 1, 1/0.6) to a later excess of females (M/F ratio cycle 5, 1/1.6).

At the time of the analysis, 16 patients were ongoing in study 2; all other patients had either completed the studies or discontinued therapy for the reasons described below. As the numbers of patients participating at each additional cycle declined from 1 cycle to the next, the reasons for withdrawal were examined and categorised into three groups (Fig. 5): i) those that could be related to poor emetic control; ii) those unrelated to control of emesis; iii) unspecified reasons. Reasons possibly related to poor emetic control were defined as: alternative antiemetic regimen administered (n = 86); patient refusal (n = 19); patient lost to follow up (n = 15); inadequate emetic control (n = 2); adverse event (redness on arms) (n = 1).

It can be seen from Fig. 5 that the majority of patients withdrew due to reasons that were not associated with poor emetic control; a total of 123/828 patients (14.9%) discontinued treatment for reasons that may have been related to poor emetic control. A further 82 patients withdrew (9.9%) for unspecified reasons.

All adverse events occurring at any time between granisetron administration and the follow-up assessment, irrespective of likely cause, were recorded. The percentage of patients reporting adverse experiences at each cycle remained fairly constant at approximately 20% for up to 7 additional cycles, dropping to 7% at the eighth (Table 2). Headache was the most common complaint affecting approximately 6% of patients and tended to be mild and transient. The second most frequent event was constipation reported by approximately 3% of patients at each additional cycle.

DISCUSSION

Maintenance of antiemetic response over repeated cycles of cancer chemotherapy is an important aspect of supportive care but few studies have specifically addressed this issue. In a controlled study involving 343 patients, the efficacy of high-dose metoclopramide regimens was found to decrease over multiple cycles of high-dose cisplatin regimens. Complete protection from nausea and/or vomiting decreased from 58.3% to 44.9% in 158 patients who completed 3 successive cycles of

Table 2. Most frequently reported adverse events by cycle of granisetron (40 μg/kg and 3 mg data combined)

	Additional cycles of granisetron							
	1	2	3	4	5	6	7	8
No. of patients	747	577	360	254	187	59	45	29
% with adverse events	19.3%	18.5%	20.3%	22.0%	21.2%	18.6%	17.7%	6.9%
Headache	6.6%	6.4%	3.9%	7.0%	7.5%	5.1%	4.4%	3.4%
Constipation	3.5%	1.6%	1.1%	1.6%	1.1%	3.4%	0	0
Abdominal pain	0.7%	1.2%	0.8%	0.8%	1.1%	0	0	0
Dyspepsia	0.8%	0.5%	0.8%	0.4%	0.5%	1.7%	0	0

cisplatin (> 50 mg/m²) [3]. However, as more than half the patients withdrew from the study, this may not be an accurate reflection of efficacy at the third cycle. In a further study of 107 breast cancer patients undergoing 6 consecutive cycles of adjuvant FAC chemotherapy, complete protection from vomiting decreased from 62.6% during the first cycle to 48.6% at the sixth, following an antiemetic cocktail regimen of methylprednisolone, thiethylperazine and amitriptyline [4].

The response to granisetron over repeated cycles of a range of cytotoxic therapies was examined in two large open-label studies involving over 800 patients. Patients who had participated in granisetron protocols at their initial cycle of chemotherapy and chose to receive granisetron for future cycles were studied. Initially a 40 μg/kg prophylactic dose of granisetron was administered, a dose shown to provide optimal antiemetic efficacy against a range of cytotoxic agents [5]. The dosage regimen was later simplified to a standard 3 mg dose for all patients (equivalent to 40 μg/kg in a 75 kg person) regardless of weight, on account of the compound's wide margin of safety.

Examination of the response by chemotherapy cycle indicated that granisetron maintained a high level of efficacy for up to 8 additional cycles of emetogenic cytotoxic agents. As expected, no differences were seen between the two granisetron treatment regimens. The apparent slight increase in complete responder rate observed with both granisetron regimens at the sixth additional cycle, can be explained by the fact that the majority of patients receiving high-dose cisplatin regimens had completed their course of treatment at additional cycle 5; therefore a greater proportion of patients participating at subsequent cycles were undergoing treatment with moderately emetogenic regimens rather than cisplatin.

When analysed by the primary cytotoxic regimen, it was evident that both granisetron doses (40 μg/kg and 3 mg) maintained efficacy at between 60% and 70% complete response during the 8 additional cycles of moderately emetogenic agents. However, there was an apparent fall-off in the efficacy of granisetron after each successive cycle of high-dose cisplatin such that by the fifth additional cycle the complete response rate had decreased from around 60% to between 30% to 45%. The analysis was cut-off after the fifth additional cycle since few cisplatin patients participated in later cycles, and therefore any analysis of the data would have yielded results of dubious significance.

It is recognised that gender influences response to antiemetics and therefore the cisplatin data were further investigated by stratifying the sex. Although the number of patients in both strata were small by the fourth and fifth additional cycles, there was a clear trend for a higher response rate in males than females throughout the cisplatin courses, consistent with previous observations following high-dose metoclopramide regimens [6]. However, in contrast to the marked reduction in efficacy noted when both sexes were combined, this trend was not so apparent in either subgroup of males or females. Further interrogation of the data revealed that the proportion of males to females reversed during the study from an initial predominance of males to a later excess of females. It would therefore appear that much of the decrease in efficacy over 5 cisplatin cycles reflects a change in the balance of males (low risk) to females (high risk). Small progressive loss of antiemetic efficacy over 5 successive cycles of cisplatin, may be related to incomplete control of acute emesis or the occurence of delayed symptoms acting as a conditioning stimulus for anticipatory vomiting at later cycles. Since the efficacy at subsequent cycles is known to be influenced by response at earlier cycles [3] enhancing the acute response to granisetron possibly by addition of a corticosteroid, or routine prophylaxis against delayed emesis, may help to sustain efficacy against cisplatin over successive chemotherapy cycles.

Any assessment of antiemetic efficacy over multiple cycles of chemotherapy must take into consideration the reasons for withdrawal from the study, otherwise, a high complete response rate at later cycles could reflect patient selection rather than true maintenance of efficacy. Approximately 15% of patients participating in either study withdrew for reasons that may have been related to inadequate emetic control and 10% for unspecified reasons. As expected, the majority of patients discontinued the studies due to completion of their chemotherapy courses, accounting for the sharp decrease in patient numbers after additional cycle 5. It is of note that the patients withdrawing for reasons possibly related to poor emetic control represented only a small proportion of the patients at each cycle classified as non-complete responders. This is a further indication that the degree of patient selection bias over the repeated courses was of a minor extent.

Granisetron at doses of either 40 μg/kg or 3 mg was well tolerated over multiple cycles of chemotherapy. There was no increase in the incidence or severity of any adverse event following repeated exposure to the compound, and the safety profile was comparable to that seen following acute treatment in chemotherapy-naive patients [7]. The most frequently occurring adverse events were headache and constipation reported with almost constant frequency at each successive cycle.

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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Fractionated Chemotherapy - Granisetron or Conventional Antiemetics?

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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.
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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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