Original article

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A randomized double-blind trial to compare the clinical efficacy of granisetron with metoclopramide, both combined with dexamethasone in the prophylaxis of chemotherapy-induced delayed emesis

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Background: The prophylactic use of 5-HT_3 receptor antagonists (setrons), after the first 24 h (acute phase) of exposure to emetic chemotherapy, to decrease the incidence of 'delayed phase' emesis increases costs. We designed a study to evaluate the efficacy of a setron (granisetron) in the delayed phase, compared with metoclopramide, each combined with a corticosteroid.

Patients and methods: Patients on their first course of single-day emetic chemotherapy (cisplatin, carboplatin, doxorubicin, cyclophosphamide and others) received granisetron 2 mg p.o. and dexamethasone 8 mg p.o. on day 1, followed for 5 days by dexamethasone 4 mg p.o. od combined with either metoclopramide 20 mg p.o. tds or granisetron 1 mg bd in a double-blinded double-dummy protocol. Patients evaluated the results using a diary card. Randomization was stratified by institution, sex, emetic chemotherapy naïve versus previous, alcohol consumption and platinum versus non-platinum regimen.

Results: 131 evaluable patients received granisetron in the delayed phase, and 127 received metoclopramide. Control of acute emesis in both arms was similar (86% granisetron; 85% metoclopramide). The 35 patients experiencing acute emesis had poor control in the delayed phase, with only four granisetron and three metoclopramide patients having no or mild nausea and no vomiting.

Conclusions: In daily practice, a combination of oral dexamethasone and oral granisetron achieves an extremely high control of acute emesis (86% protection). Our data suggest that routine prescription of setrons for delayed phase control is not advisable as it increases costs without any benefit for the majority of patients. Delayed emesis in the rare patients with acute phase emesis remains an unsolved problem.

Key words: acute, delayed, dexamethasone, granisetron, nausea, vomiting

Introduction

The combination of a 5-hydroxytryptamine$_3$-receptor antagonist (referred to as a 'setron' in this paper) with a corticosteroid is the recommended standard for prevention of acute emesis caused by moderately to highly emetic chemotherapy [1]. Recent results have shown that a combination of oral granisetron and oral dexamethasone was as effective as i.v. high-dose ondansetron and dexamethasone agents in this indication [2, 3]. However, the administration of highly and moderately emetic cytotoxic agents causes nausea and vomiting not only within 24 h after the start of chemotherapy (acute emesis), but also during the following days (delayed emesis). Setrons are not universally accepted as a standard in preventative treatment of delayed emesis, in spite of some positive studies [1]. This might be due to methodological problems, as many studies did not take acute emesis into account as a predictive factor for delayed emesis.

With this background, the Swiss Group for Clinical Cancer Research (SAKK) designed a study to evaluate the efficacy of a setron in the delayed emesis phase, compared with metoclopramide, both agents being combined with a corticosteroid. Patients receiving moderately to highly emetic cytotoxic agents were given oral granisetron and oral dexamethasone on the day of chemotherapy and then randomly assigned to one of two oral treatments for the prevention of delayed emesis: dexamethasone with either granisetron or metoclopramide. This trial was activated on 28 May 1996 and closed for patient accrual on 30 April 1999. The main end point of the trial was to compare the clinical

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efficacy and safety of granisetron and metoclopramide in combination with dexamethasone in the prophylaxis of delayed nausea and vomiting induced by emetic cancer chemotherapy. This final report gives a complete analysis, and is based on information from all 267 randomized patients.

Patients and methods

The trial was open to all patients receiving their first course of moderately or highly emetic single-day chemotherapy, and was approved by the local Institutional Review Boards. Patients were given a written informed consent form, and if they accepted, were randomized into the trial. The design was intended to reflect the reality of daily practice. Therefore, instead of stating that the delayed phase of treatment and observation started 24 h after the initial treatment, the next morning was used as the time point to begin treatment against possible delayed emesis. All patients were treated with granisetron 2 mg and dexamethasone 8 mg p.o. for the prevention of acute emesis, on day 1. Then, they were treated with a moderately to highly emetic chemotherapy regimen containing cisplatin ≥50 mg/m^2, carboplatin ≥300 mg/m^2, dacarbazine ≥500 mg/m^2, doxorubicin ≥40 mg/m^2, epirubicin ≥60 mg/m^2, ifosfamide ≥1200 mg/m^2, cyclophosphamide ≥600 mg/m^2 and/or irinotecan ≥300 mg/m^2, on day 1. On subsequent days, the patients could receive chemotherapy containing etoposide or 5-fluorouracil, which are considered not to influence delayed emesis. After the acute-phase therapy, patients received a package containing unblinded dexamethasone 4 mg mornings and evenings on days 2–6 and the blinded antiemetic oral study treatment for the same 5 days, consisting of either granisetron 1 mg mornings and evenings and a placebo at lunch time, or metoclopramide 20 mg tds. With the help of the hospital team, patients also completed the first page of a four-page diary card on which they had to indicate daily for days 1–6 whether they experienced any nausea or vomiting or other side-effects. The diary card and detailed analyses of the various indicators of patient burden are reported elsewhere [4]. On day 7, patients mailed the completed diary to the Swiss Institute for Applied Cancer Research Coordinating Center using a prestamped envelope, no further documentation on the patients was necessary except for a brief overview of toxicity at their next clinical visit and verification of the returned pillbox. On 30 October 1997, after randomization of 124 patients, an amendment to the protocol was activated, introducing a 'back-up' question on delayed nausea or vomiting to be asked at the first follow-up visit by the treating physician. This was necessary in order to assess the main end point (delayed emesis) in those patients who did not return their diary card.

The main end point of the trial was control of emesis, defined as only the most mild nausea (not interfering with normal daily life) and no vomiting over the period of 5 days after emetic chemotherapy. The primary evaluation of this main end point was restricted to the group of patients with control of acute emesis (for 18–24 h after treatment), but an intention-to-treat analysis irrespective of control of acute emesis was also planned.

Randomization by the minimization method was stratified by institution; sex; chemotherapy naïve versus previous chemotherapy; regular alcohol consumption (daily intake of >2 dl wine and/or >5 dl beer and/or >1 measure of spirits), yes versus no; and chemotherapy regimen, cisplatin or carboplatin versus others.

Statistics

The trial was planned to have a size that would be sufficient to detect an absolute difference of 20% in the rates of control between the two arms for the patients without acute phase emesis. It was calculated that a maximum of 270 patients without emesis in the acute phase was necessary to test such a difference with a two-sided significance level of 5% and 90% power. This number could be lower if the rate of control was markedly >50%. In order to account for 25% of patients having acute emesis, the sample size was raised to 360 patients. The analysis of the main end point was to be by intention-to-treat.

No formal interim analysis was planned in the protocol. Nevertheless, the trial team decided to perform one in March 1999, after randomization of 257 patients, because of a problem with the trial medication: the expiry date was 29 April 1999. The intention was to determine whether there was sufficient need to continue the trial to the planned accrual goal of 360 patients. If the chance of reaching a significant difference in the main outcome was remote, then there would not have been sufficient reason for investing more resources in the trial by preparing new trial medication.

The interim analysis showed that the differences between the two treatments were minimal and the formal interim test showed clearly that the continuation of the trial would have been extremely unlikely to lead to a difference of 20% between the treatment arms in terms of control, which could be detected with a power of 90%. After seeking the opinion of independent experts who concurred with our analysis, this led to the conclusion that the trial could be stopped safely without incurring any loss of information with regard to the research question posed in the protocol.

A second consideration justified stopping the trial at that time. The overall rate of control (~80%) was higher than anticipated at the time of planning the trial (60–70%). This meant that the cautious approach to sample size estimation in the protocol could be revised, clarifying that not more than 230 evaluable patients without acute emesis were needed to test for a difference of 20% in control. Furthermore, taking into account that only ~14% of all patients experienced acute emesis (not 25% as estimated in the protocol), the revised sample size would have been 267 fully evaluable patients [230 × 1/(1–0.14)], a number which was almost reached. In reality, 230 evaluable patients without acute emesis is a slight under-estimate, because only one interim analysis was carried out. The exact number would have been 238.

Several statistical tests were performed in a descriptive way. However, the primary evaluation of the main end point by the chi-square test was carried out in a formal way and took into account that interim testing affects the significance level of the final analysis. An α-spending function was chosen according to the O'Brien–Fleming procedure [5] with Lan–deMets boundaries [6]. This is a very conservative procedure and leads to early stopping only in a case with strong evidence that continuation is not warranted. The calculation was performed with the statistical package EaSt (1995, Cytel Corp, Cambridge, MA). Specifically, a post-hoc trial design was generated with EaSt allowing for one interim evaluation with early stopping in the case of either a statistically significant difference between the treatment arms or sufficient evidence that no statistical significance will be reached by proceeding up to the original target sample size. A significance level of 5% and a power of 90% for a chi-square test for the comparison of two proportions (80% versus 60%) were chosen as the basis for the evaluation of the main end point. The P value for partial control of delayed emesis in patients without acute emesis was 0.54, it was therefore concluded that the likelihood of reaching a statistically significant difference by including more patients was extremely small. It was therefore decided to stop the trial at the end of April 1999.

Results

A total of 267 patients from six institutions (106 from St Gallen, 76 from Ticino, 67 from Geneva-Genolier, three from Aargau, three from Chur, all in Switzerland and three from the European Institute of Oncology, Milano, Italy) were randomized. For nine patients (3%; three patients on granisetron and six on metoclopramide) no information on acute and delayed emesis was available; these nine could not be evaluated. The analysis is therefore based on 258 patients.

Patient characteristics

The distribution of parameters for stratification at randomization is shown in Table 1. Two patients were stratified wrongly because their chemotherapy regime was incorrectly specified on the eligibility form. Despite the exclusion of nine patients who had no data about delayed emesis, the stratification parameters were well balanced between the two treatment arms. Other patient characteristics are shown in Table 2.

Table 1. Stratification factors

	Granisetron (n = 131)	Metoclopramide (n = 127)
Sex		
Male	46 (35%)	46 (36%)
Female	85 (65%)	81 (64%)
Chemotherapy		
Naïve	123 (94%)	120 (94%)
Previous	8 (6%)	7 (6%)
Regular alcohol consumption[a]		
Yes	20 (15%)	20 (16%)
No	111 (86%)	107 (84%)
Chemotherapy regimen		
Cisplatin/carboplatin	76 (57%)	69 (54%)
Cisplatin	35 (27%)	28 (22%)
Carboplatin	41 (31%)	41 (33%)
Others	57 (43%)	58 (46%)

[a]Regular alcohol consumption was defined as a daily intake of >2 dl wine and/or >5 dl beer and/or >1 measure of spirits.

Table 2. Patient characteristics at randomization

	Granisetron (n = 131)	Metoclopramide (n = 127)
Age (years)		
Median	58	57
Range	24–84	19–90
Performance status		
0	101 (77%)	104 (82%)
1–2	30 (23%)	23 (18%)
Site of tumor (>1 possible)		
Breast	39 (30%)	45 (35%)
Lung	23 (18%)	34 (27%)
Gastric	6 (5%)	9 (7%)
Other gastrointestinal	3 (2%)	5 (4%)
Other sites[a]	60 (46%)	36 (28%)

[a]Other tumor sites were bladder, cervix, head and neck, lung, oesophagus, lymphoma, ovary, seminoma, skin, urogenital, lung and testis, and two with unknown primary.

In six out of 258 cases (2%; four on granisetron and two on metoclopramide) the patients did not receive the antiemetic treatment for the acute phase as prescribed in the protocol: one received only dexamethasone and no granisetron, three had granisetron alone, one had 4 mg of dexamethasone, and one had methylprednisolone and tropisetron. One patient was randomized on the day after chemotherapy, which is an eligibility violation. Four patients had neuroleptics, 22 patients benzodiazepines, and 43 patients had pain-relievers as concurrent medication.

Diary cards

Out of the 258 patients, 250 (97%) returned the diary card to the Coordinating Center. The diary card of one patient had to be discarded because the patient did not fill in the card himself. From the remaining 249 patients, 58 did not answer all the questions, and 191 (77%) returned a complete diary.

Acute emesis

Table 3 shows the rate of acute emesis on day 1, as reported by the patients on the diary card (one patient provided no information). Thus the rate of acute emesis (14% severe nausea or vomiting) was lower than the 20–25% anticipated in the protocol, confirming the high degree of protection from acute emesis obtained with a setron and a corticosteroid combination previously reported by others [1].

A total of 28 patients had reported nausea or vomiting on the day before treatment. They were well balanced between the treatment arms. Two of them had vomited, and these two continued to vomit under treatment (one in each arm). Of the five with severe nausea but no vomiting, two had no vomiting and minimal nausea on the day of treatment under granisetron. A more detailed analysis shows that acute emesis was lower under carboplatin than any other regimen, and equal in the patients treated with cisplatin or other agents (Table 4). There were no significant differences in the control of acute emesis between the two arms. Thus, the results of the delayed phase are not influenced by a difference in control during the acute phase, which may have been the case as patients with acute emesis are much more likely to experience delayed emesis.

Delayed emesis

Control of delayed emesis (equivalent to the most mild nausea and no vomiting) on days 2–6 is shown in Table 5. This table is based on 248 patients, as we did not have data about acute phase control for three patients on carboplatin, two on cisplatin and five on other chemotherapies.

The primary end point was control of emesis during the delayed phase in patients having control during the acute phase. This comparison does not show any difference between the treatment arms (Table 6). The comparison for all patients is based on all 258 for whom the end point could be assessed either from the diary card (n = 248) or from the back-up question (n = 10). Both tests are clearly not significant. The post-hoc power for the comparison, when restricted to patients without acute emesis, is

Table 3. Acute emesis control

Acute emesis	Granisetron (n = 129)	Metoclopramide (n = 119)	Total (n = 248)
None	88 (68%)	80 (67%)	168 (68%)
Mild nausea, no vomiting	23 (18%)	22 (18%)	45 (18%)
Severe nausea, no vomiting	4 (3%)	6 (5%)	10 (4%)
Vomiting with or without nausea	14 (11%)	11 (9%)	25 (10%)

Day 1 antiemetic regimen: granisetron 2 mg and dexamethasone 8 mg p.o.

Table 4. Acute emesis by chemotherapeutic agent

	Granisetron	Metoclopramide	Total
Cisplatin	n = 34	n = 26	n = 60
None	21 (62%)	17 (65%)	38 (63%)
Mild nausea, no vomiting	5 (15%)	3 (12%)	8 (13%)
Severe nausea, no vomiting	3 (9%)	1 (4%)	4 (7%)
Vomiting with or without nausea	5 (15%)	5 (19%)	10 (17%)
Carboplatin	n =40	n = 40	n = 80
None	36 (90%)	33 (83%)	69 (86%)
Mild nausea, no vomiting	4 (10%)	6 (15%)	10 (13%)
Severe nausea, no vomiting	0	1 (3%)	1 (1%)
Vomiting with or without nausea	0	0	0
Other agents	n = 55	n = 53	n = 108
None	31 (56%)	30 (57%)	61 (56%)
Mild nausea, no vomiting	14 (25%)	13 (25)	27 (25%)
Severe nausea, no vomiting	1 (2%)	4 (8%)	5 (5%)
Vomiting with or without nausea	9 (16%)	6 (11%)	15 (14%)

88%. The confidence intervals for partial control in the two treatment arms overlap to a large extent.

Subgroup analyses

Control of delayed emesis (defined as the most mild nausea and no vomiting) according to the three categories of emetic chemotherapy is shown in Table 7. Control of delayed emesis is very similar between the treatment arms. The rate of control is 51% under cisplatin, and 72% and 75%, respectively, under carboplatin and other chemotherapeutic agents.

Toxicity

Toxicities during antiemetic treatment, other than nausea or vomiting, were reported on the diary card by the patients and on a predesigned form filled in by the investigator team at the next visit to the hospital, these are summarized in Table 8. It can be observed that more patients reported abnormal body-part movements on the setron; we would have expected the question (designed to capture extrapyramidal side-effects) to be more frequently positive in the metoclopramide arm. Constipation seems, as expected, to be more frequent among patients in the setron arm.

Discussion

The primary goal of this study was to observe whether patients without acute emesis benefited from a setron, compared with metoclopramide, each in combination with a corticosteroid, for control of delayed emesis. In our study, the rate of control of acute emesis by granisetron 2 mg p.o. and dexamethasone 8 mg p.o. was very high and similar in both delayed phase study arms (86% granisetron and 85% metoclopramide). These well controlled patients also had control of delayed emesis in 81% of granisetron and 84% of metoclopramide treated cases. We thus confirm that preventative treatment of delayed emetic-chemotherapy-induced nausea and vomiting depends on the rate of control during the acute phase of treatment. The 35 patients experiencing acute emesis had poor control in the delayed phase, as only four (23%) granisetron and three (18%) metoclopramide patients had no or mild nausea and no emesis. The analysis tables we provide allow the reader to have a full understanding of the results, specially in relation to the rate of acute control and its influence on delayed emesis, per type of chemotherapy and randomization. Such tables should be available for all studies of delayed emesis, as obviously these variables play a major role in the overall results.

Table 5. Maximum emesis on days 2–6 (delayed phase), according to degree of control on day 1

Degree of control on day 1	Granisetron	Metoclopramide	Total
Vomiting or severe nausea on day 1	*n* = 18	*n* = 17	*n* = 35
Degree of control on days 2–6			
No nausea or vomiting	1 (6%)	1 (6%)	2 (6%)
Mild nausea, no vomiting	3 (17%)	2 (12%)	5 (14%)
Severe nausea, no vomiting	6 (33%)	4 (24%)	10 (29%)
Vomiting with or without nausea	8 (44%)	10 (59%)	18 (51%)
No vomiting, up to mild nausea on day 1	*n* = 111	*n* = 102	*n* = 213
Degree of control on days 2–6			
No nausea or vomiting	61 (55%)	56 (55%)	117 (55%)
Mild nausea, no vomiting	29 (26%)	30 (29%)	59 (28%)
Severe nausea, no vomiting	10 (9%)	7 (7%)	17 (8%)
Vomiting with or without nausea	11 (10%)	9 (9%)	20 (9%)

Table 6. Control of delayed emesis (no vomiting, up to mild nausea) on days 2–6, in patients with control on day 1 (primary study end point) and all patients (intention-to-treat)

Patient category	Granisetron	Metoclopramide	Chi-square test
No vomiting, up to mild nausea on day 1	*n* = 111	*n* = 102	
Control on days 2–6	90 (81%)	86 (84%)	*P* = 0.53
95% confidence interval	73% to 88%	76% to 91%	
All patients (intention-to-treat)	*n* = 131	*n* = 127	
Control on days 2–6	96 (73%)	95 (75%)	*P* = 0.78
95% confidence interval	65% to 81%	66% to 82%	

Table 7. Delayed emesis by chemotherapeutic agent

	Granisetron	Metoclopramide	Total
Cisplatin	*n* = 35	*n* = 28	*n* = 63
None	13 (37%)	11 (39%)	24 (30%)
Mild nausea, no vomiting	6 (17%)	7 (25%)	13 (21%)
Severe nausea, no vomiting	4 (11%)	1 (4%)	5 (8%)
Vomiting with or without nausea	12 (34%)	9 (32%)	21 (33%)
Carboplatin	*n* = 41	*n* = 41	*n* = 82
None	24 (59%)	24 (59%)	48 (59%)
Mild nausea, no vomiting	11 (27%)	11 (27%)	10 (13%)
Severe nausea, no vomiting	4 (10%)	4 (10%)	8 (10%)
Vomiting with or without nausea	2 (5%)	2 (5%)	4 (5%)
Other agents	*n* = 55	*n* = 58	*n* = 113
None	27 (49%)	27 (47%)	54 (48%)
Mild nausea, no vomiting	15 (27%)	15 (26%)	30 (27%)
Severe nausea, no vomiting	8 (15%)	6 (10%)	14 (12%)
Vomiting with or without nausea	5 (9%)	10 (17%)	15 (13%)

Table 8. Toxicities during antiemetic treatment, including those reported by diary-card or by the investigator

Toxicity	Granisetron (n = 130)	Metoclopramide (n = 126)	Total
Epigastric pain	8 (6%)	7 (6%)	15 (6%)
Restlessness	3 (2%)	6 (5%)	9 (4%)
Abnormal body-part movements	6 (5%)	3 (2%)	9 (4%)
Sleeplessness (unusual for patient)	7 (5%)	13 (10%)	20 (8%)
Constipation (unusual for patient)	50 (38%)	37 (29%)	87 (34%)
Headaches (unusual for patient)	23 (18%)	22 (17%)	45 (18%)
Unexpected asthenia	10 (8%)	11 (9%)	21 (8%)
Any other	30 (24%)	34 (28%)	64 (26%)
Any toxicity	81 (62%)	81 (64%)	162 (63%)

Results missing from two patients.

Our study does not allow one to conclude with confidence regarding a lack of difference between the approaches in patients who had nausea and vomiting on day 1, as the numbers are small. However, other studies have not shown any superiority of the addition of a setron to dexamethasone for these patients [7, 8]. The Italian Group for Antiemetic Research has shown that for patients receiving cisplatin-based chemotherapy who have no acute emesis metoclopramide and ondansetron are of similar efficacy during the delayed phase [7]. In those patients who had acute emesis ondansetron prevented delayed emesis in only 29% of cases, compared to 4% for metoclopramide. However, if one accounts for severe nausea, no difference is observed between the arms during the delayed phase.

In patients undergoing moderately emetic chemotherapy who experienced acute emesis the Italian Group compared oral placebo to oral ondansetron 8 mg, both combined with dexamethasone 4 mg p.o. bd, on days 2–5 after the start of chemotherapy [8]. The delayed complications were prevented in 18 of the 44 patients taking the combination of the two drugs (41%) and in 10 of the 43 patients on dexamethasone alone (23%). The authors concluded, as we do, that the best choice for preventing delayed nausea and vomiting in patients at high risk for these complications remains to be identified. Other papers offer contradictory results in the field, but they were not prospectively designed to take into account the influence of acute emesis on the rate of control of delayed emesis [1, 9].

Many patients in our study had moderately emetic chemotherapy and an excellent rate of acute control with granisetron 2 mg and dexamethasone. However, emerging data indicate that a 1 mg granisetron oral dose may be sufficient for such patients [10]. The 8 mg dose of dexamethasone used in this study for acute emetic control might be too low for patients receiving cisplatin-based chemotherapy, where 20 mg has been suggested as a standard [11]. However, for the majority of our patients this combination was excellent, with an 84% acute control rate. The doses of dexamethasone and metoclopramide used in this study are not those suggested by other authors for use with cisplatin-based chemotherapy [12]. They are based on a clinical practice consensus, but may be less effective than the doses others have suggested. Should this be the case, it would only reinforce our main message: setrons are of very limited value in control of delayed nausea and vomiting.

The routine prescription of setrons for delayed phase control is not advisable as it increases costs without any benefit for the majority of patients. Patients should be offered a combination of a corticosteroid and metoclopramide, for a duration which has not yet been firmly established as it varies from 3 to 5 days among the available studies. Delayed emesis in the rare patients with acute phase emesis remains an unsolved problem. The development of neurokinin-1 receptor antagonists might be of major importance in this setting [13].

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