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Optimal combination therapy with Navoban® (tropisetron) in patients with incomplete control of chemotherapy-induced nausea and vomiting

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Even with the availability of potent and selective serotonin antagonists, chemotherapy-induced nausea and vomiting remain a major problem for many patients. This study aims to evaluate the benefit of combination therapy based on Navoban® (tropisetron) in patients who had incomplete control of nausea and/or vomiting induced by chemotherapy when using Navoban® as a single antiemetic agent. In their first chemotherapy course, 1072 patients planned to receive at least two identical cycles of emetogenic chemotherapy were treated with 5 mg Navoban® once daily. To evaluate three treatments additional to the recommended 5 mg once-daily Navoban® regimen during Course 2 in those patients who had shown incomplete control of nausea and/or vomiting on any day of Course 1, a 2 x 2 x 2 factorial design was employed. Of these patients, 445 were centrally randomised to receive an additional dose of open-label dexamethasone (Day 1, 0.2 mg/kg i.v.; Days 2–6, 8 mg p.o.) and/or open-label alizapride (Day 1, 100 mg i.v. and 4 x 50 mg p.o.; Days 2–6, 4 x 5 mg p.o.) and/or double-blind Navoban® – that is, doubling the dose to 10 mg once daily – or placebo. Complete response rates during Course 1 (CRR, no nausea and no vomiting) were, for Day 1, 72% and for Days 1–6, 48%. More complete responders were observed when dexamethasone was added during Course 2, both on Day 1 (76% vs. 66%, $p = 0.020$) and on Days 1–6 (50% vs. 34%, $p = 0.0004$). With the addition of a conventional dose of alizapride, a moderate increase in CRR was observed; this was 75% vs. 68% ($p = 0.14$) on Day 1 and 47% vs. 37% ($p = 0.041$) on Days 1–6. CRR was not altered when the Navoban® dose was doubled. In patients incompletely controlled with Navoban® alone, the addition of dexamethasone significantly increased the CRR of both acute and delayed emesis (see Discussion).

Key words: Navoban® (tropisetron), nausea, vomiting/emesis, alizapride, dexamethasone.

Introduction

Serotonin (5-hydroxytryptamine$_3$, 5-HT$_3$) receptors, located in the chemoreceptor trigger zone of the area postrema and in the gastrointestinal tract, are held to be the mediators of emesis induced by chemotherapy. The fact that the dopamine D_2-antagonist metoclopramide, given in high doses, is also a serotonin antagonist[1] which probably owes its antiemetic effect to the blockade of this 5-HT$_3$-receptor, underscores the importance of this mechanism in the emetic response. A number of selective and potent serotonin antagonists have become available during the last few years, and their important role in the suppression of acute emesis induced by chemotherapy has been established.[2,3] Despite this advance, the control of nausea and vomiting remains incomplete in a large number of patients; this applies not only to the first 24 hours of chemotherapy but also to the subsequent days (delayed nausea and vomiting).[4,5]

Combination therapies with serotonin antagonists have been investigated in an effort to improve the response still further. It seems probable that clinical effectiveness for the serotonin antagonists, given with either corticosteroids or dopamine D_2-antagonists, has increased,[6] although it is not yet known whether the addition of both types of agent might enhance the response yet further.

One agent which has proved to be remarkably

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effective in the prevention of vomiting induced by emetogenic chemotherapy is Navoban® (tropisetron), a potent and selective 5-HT_3-receptor antagonist.[5] The study reported here aimed to assess the benefit of combination therapy with Navoban® in patients with incomplete control of nausea and vomiting when this compound was used as a single antiemetic agent. In addition, we evaluated the effects of both dexamethasone and a conventional dose of the D_2-receptor antagonist, alizapride. Moreover, we were curious to find out whether incomplete responders would benefit from a double dose of Navoban®. These three questions were addressed using a single trial based on a factorial study design.[7]

Materials and methods

One thousand and seventy-two oncology patients (639 women and 433 men) with a median age of 59 years (range 17–88 years) participated in the study, which took place between March 1992 and June 1993 in 44 centres in Belgium. All patients gave their informed consent and the study was approved by the institutional review boards.

Eligibility criteria

Chemotherapy-naive inpatients and outpatients participated in the trial; each patient was planned to receive at least two identical cycles of emetogenic chemotherapy, for a maximum duration of 5 days and separated by 2 weeks, for up to 2 months. It was essential that the chemotherapy regimen contained at least one of the following drugs at the dose indicated:

cisplatin (CDDP)		≥ 50 mg/m² in one day
	or	≥ 75 mg/m² per course
cyclophosphamide		≥ 600 mg/m²
cytarabine		≥ 500 mg/m²
ifosfamide		≥ 1000 mg/m²
carboplatin		≥ 300 mg/m²
epirubicin		≥ 70 mg/m²
adriamycin		≥ 50 mg/m²
	or	≥ 25 mg/m² in combination
mitoxantrone		≥ 10 mg/m² in combination
mitomycin C		≥ 10 mg/m² in combination
or *mustine, carmustine, dactinomycin* or *dacarbazine*		in any dose

In the second course, reductions of up to 25% of chemotherapy dose – for reasons other than gastrointestinal toxicity – were tolerated. Patients were deemed ineligible if they suffered from severe hepatic, renal or cardiac insufficiency; had tumour involvement of the CNS; were receiving concomitant radiotherapy or immunotherapy; were being treated with chemotherapy regimens containing corticosteroids; were taking any other medication that could influence nausea and vomiting apart from small doses of benzodiazepines given at night; or had received any other investigational drug.

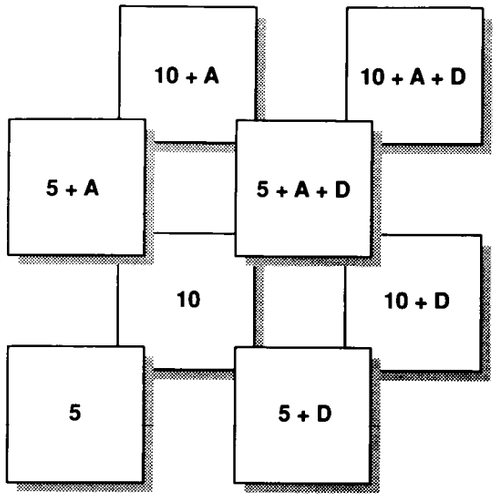

Figure 1. Factorial design (2 x 2 x 2): 5 = 5 mg Navoban®; 10 = 10 mg Navoban®; A = alizapride; D = dexamethasone.

Treatments

The recommended regimen given to all patients during their first course of chemotherapy was 5 mg Navoban® once daily.[8] On Day 1, a single dose of 5 mg Navoban® was administered intravenously in 100 ml saline over 15 minutes before chemotherapy, and as a single 5 mg morning dose (orally) over the 5 following days. Those who did not remain totally free from both nausea and vomiting during the full observation period (Days 1–6) of this first course (the incomplete responders) were randomised for a second course in a three-way (2 x 2 x 2) factorial design to three treatments in addition to the 5 mg once-daily regimen of Navoban® (Figure 1).

The additional treatments were:

- *open-label dexamethasone* (DXM)
  Day 1, 0.2 mg/kg i.v.; Days 2–6, 8 mg p.o.

and/or

- *open-label alizapride*
  Day 1, 100 mg i.v. and 4 x 50 mg p.o.;
  Days 2–6, 4 x 50 mg p.o.

and/or

- *double-blind Navoban®*
  Day 1, 5 mg i.v.; Days 2–6, 5 mg p.o.
  or matching *placebo*

There were therefore eight distinct treatment groups, corresponding to every possible combination of the three additional treatments. However, for the purpose of statistical analysis, the three primary comparisons planned for the study were:

- all treatment groups receiving dexamethasone vs. those which did not;
- all treatment groups receiving alizapride vs. those which did not;
- the 10 mg Navoban® vs. the 5 mg Navoban® groups.

The random allocation of patients to one of the eight treatment groups was achieved with a central computer system using a modified version of Pocock and Simon's minimisation procedure.[9] The variables which follow were communicated by telephone and taken into account by the minimisation procedure:

- centre
- sex
- diagnosis (breast cancer, ovarian cancer, lung cancer or other)
- alcohol abuse (yes or no)
- cisplatin dose ≥ 100 mg/m^2 (yes or no)
- response during the first course (partial response or failure).

Alcohol abuse was defined as the consumption of more than 5 glasses of alcoholic drink per day – the equivalent of a total daily intake of 50 or more grammes of alcohol.

Evaluation of response

Our method of measuring nausea and vomiting was comparable to that employed by Schmidt *et al.*[5] The number of hours of nausea and the number of vomits (including retches) were recorded on a patient diary card for each of Days 1–6 of both chemotherapy courses. If, during the 24-hour period, neither nausea nor vomiting occurred, the response for that day was recorded as 'complete'. A 'partial' response was recorded if over the 24-hour period the patient reported 1 to 4 vomits and/or less than 4 hours of nausea. All other responses were classed as 'failures'. For the total course (Days 1–6), response was graded as 'complete' when neither reaction occurred during the six days; 'partial' as a partial response on any day, and with no 'failure' days; and 'failure' on any day or 'partial' with more than 12 hours of nausea in total.

Statistical methods

Three hundred and forty randomised patients were required to make up the minimum sample size defined by the protocol, to give the study a power of 80% at the 5% significance level to detect a 15% improvement for complete response rate for Days 1–6 of Course 2 (from 35% to 50%). We continued to enrol patients until we had randomised a sufficient number, taking into account a safety margin of 20% for possible violations of protocol.

The analyses were done in two groups:

- descriptive statistics for all patients entered in the study (n = 1072); and
- inferential statistics for the randomised patients who completed Course 2 (n = 445).

We present three analyses for randomised patients:

- dexamethasone vs. no dexamethasone;
- alizapride vs. no alizapride;
- 5 mg Navoban® vs. 10 mg Navoban®.

An intention-to-treat approach was used to provide the primary data analysis of all randomised patients who completed both courses.

Moreover, identical comparisons were made for patients who were deemed fully evaluable by adequate compliance to protocol throughout the courses.

The two primary response variables were percentage of randomised patients experiencing total control of nausea and vomiting during the first 24 hours (Day 1) and over the complete course (Days 1–6).

The stratified permutation test[10] was used to compare the response rates of the two groups, which were stratified by use or non-use of the other treatments. Each test was two-sided and, in accordance with the factorial form of the design, adjustments were not made to the p-values of the statistical tests employed to compare either treatment in its control group.[7] All the same, because two primary end-points were analysed, a p-value smaller than 0.03 for either end-point was deemed statistically significant so as to sustain an overall alpha-level of 0.05. Moreover, the primary efficacy variables reported 95% confidence intervals (CI).

For the analysis we used SAS, version 6.08 (under licence from the SAS Institute in Cary, North Carolina, USA) and StatXact, version 2.0 (under licence from the CYTEL Software Corporation, Cambridge, Mass., USA).

Results

Breast cancer was the most frequent diagnosis requiring chemotherapy in our study population, followed

Table 1. Protocol violations and early administration of rescue treatment

	Random patients (n = 460)	Not random patients (n = 612)	All patients (n = 1072)
Minor protocol violations			
Courses < 14 days apart	2	7	9
Chemotherapy after Day 5	2	3	5
Chemotherapy dose < 90% of protocol	13	37	50
Chemotherapy different in Course 2	12	18	30
Dose reduction > 25% in Course 2	14	19	33
Patients with any minor protocol violation *	38	78	116
Major protocol violations / early rescue treatment (ERT) in Course 2			
Chemotherapy before study	0	5	5
Radiotherapy during study	4	7	11
Systemic corticosteroids during study	18	13	31
ERT in Course 2	9	2	11
Any major protocol violation or ERT *	29	27	56
Patients with any protocol violation *	63	99	162

* Some patients had multiple protocol violations.

by lung cancer (22%), cancer of the head and neck (11%) and ovarian cancer (11%). All patients had a Karnofsky status of at least 60; indeed, 80% had a Karnofsky status ≥ 80; and 59% of all patients received chemotherapy on a single day. We used combination chemotherapy in 97% of all patients, while 47% received two different agents and 47% received three.

The agents used in the first course were:

- cyclophosphamide (used in 47% of all patients)
- 5-fluorouracil (38%)
- carboplatin (35%)
- epirubicin (26%)
- cisplatin (20%)
- etoposide (16%)
- doxorubicin (11%)
- mitoxantrone (11%)
- ifosfamide (11%)

Agents used in fewer than 10% of the courses were:

- methotrexate (8%), vindesine (7%), mitomycine (6%), vincristine (5%)
- bleomycin
- vinblastine
- dacarbazine
- carmustine
- dactinomycin
- lomustine
- mustine
- vinorelbin
- thiotepa
- teniposide

In 162 patients, protocol violations or administration of rescue treatment after less than 5 hours of nausea and no vomiting were observed (Table 1). Patients who had received chemotherapy before the study, and those who received concomitant radiotherapy or systemic corticosteroids, were regarded as major protocol violators.

We achieved response results for a total of 1059 patients for the first course. Of these, 72% had complete response, with neither nausea nor vomiting on the first day, and 48% (n = 513) with neither reaction over the whole course (Days 1–6). Days 2 and 3 had the lowest complete responses (61% and 62%). For Course 1, 268 patients (25%) had partial response and 278 (26%) a failure. Forty-five of the 546 incomplete responders who were ineligible for randomisation were not randomised, while 49 left the study before this procedure, for a variety of reasons, including death from the progression of the disease, incompliance, change in chemotherapy regimen, addition of radiotherapy or other violations of protocol. Of these 94 patients (43%), 40 had a partial response for Course 1 and 54 (57%) a failure.

The 460 patients who received randomised treatment included 6 with complete response for Course 1 and 2 patients with unknown response in Course 1. Thirteen, evenly distributed over their allocated treatment groups, despite being randomised, did not begin the second course and were taken out of the study because of adverse events (n = 5), incompliance (n = 3) or protocol violations (n = 3), or because they

Table 2. Distribution of prognostic factors across the eight subgroups (randomised patients)

Patients (N = 445)	N = 57	N = 56	N = 56	N = 56	N = 56	N = 56	N = 52	N = 56
Navoban® (tropisetron)	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg
Dexamethasone	No	No	Yes	Yes	No	No	Yes	Yes
Alizapride	No	No	No	No	Yes	Yes	Yes	Yes
Cancer type								
Breast	24 (42%)	22 (39%)	23 (41%)	23 (41%)	24 (43%)	23 (41%)	24 (46%)	24 (43%)
Ovarian	7 (12%)	6 (11%)	6 (11%)	5 (9%)	5 (9%)	7 (13%)	5 (10%)	7 (13%)
Other	26 (46%)	28 (50%)	27 (48%)	28 (50%)	27 (43%)	26 (46%)	23 (44%)	25 (45%)
Sex								
Male	19 (33%)	18 (32%)	20 (36%)	18 (32%)	19 (34%)	18 (32%)	16 (31%)	18 (32%)
Female	38 (67%)	38 (68%)	36 (64%)	38 (68%)	37 (66%)	38 (68%)	36 (69%)	38 (68%)
Alcohol abuse								
Yes	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	1 (2%)	0 (0%)
No	57 (100%)	55 (98%)	56 (100%)	56 (100%)	55 (98%)	55 (98%)	51 (98%)	56 (100%)
CDDP dose								
≥ 100 mg/m²	7 (12%)	6 (11%)	7 (13%)	8 (14%)	7 (13%)	7 (13%)	5 (10%)	6 (11%)
< 100 mg/m²	50 (88%)	50 (89%)	49 (88%)	48 (86%)	49 (88%)	49 (88%)	47 (90%)	50 (89%)
Resp. Course 1								
Partial	30 (53%)	30 (54%)	29 (52%)	29 (52%)	29 (52%)	30 (54%)	26 (50%)	29 (52%)
Failure	27 (47%)	26 (46%)	27 (48%)	27 (48%)	27 (48%)	26 (46%)	26 (50%)	27 (48%)
Chemotherapy *								
Fractionated	38 (67%)	37 (66%)	36 (64%)	39 (70%)	34 (61%)	39 (70%)	34 (65%)	35 (63%)
Unfractionated	19 (33%)	19 (34%)	20 (36%)	17 (30%)	22 (39%)	17 (30%)	18 (35%)	21 (38%)
CDDP treatment *								
None	43 (75%)	43 (73%)	41 (73%)	40 (71%)	39 (70%)	47 (84%)	40 (77%)	46 (82%)
Single day	6 (11%)	8 (14%)	6 (11%)	8 (14%)	6 (11%)	4 (7%)	6 (12%)	3 (5%)
Multiple day	8 (14%)	5 (9%)	9 (16%)	8 (14%)	11 (20%)	5 (9%)	6 (12%)	7 (13%)

* Not included in the minimisation procedure.

considered the study medication ineffective (n = 2). Among the protocol violations were changes in chemotherapy planning or the addition of radiotherapy.

For all but 2 of the 447 randomised patients who started the second course, efficacy results were available. Nineteen subjects stopped medication early, because they considered the study medication ineffective (n = 10), or because of adverse events (n = 4), incompliance (n = 2) or protocol violations (n = 3). These 19 were included in every analysis and were evenly distributed over the eight treatment groups.

Efficacy analysis of the randomised patients was also performed on patients with no major violations of protocol (n = 421). The results – not shown in this paper – were virtually identical with those of the intention-to-treat group.

The group of randomised patients consisted of 309 women (68%) and 151 men (32%) with a median age of 58 years (age range 17–80 years). Breast cancer was the most frequently diagnosed malignancy (40%), followed by lung cancer (21%), ovarian cancer (11%) and head and neck cancer (7%). Cisplatin-containing therapy was administered to 24% of the randomised patients, with a cisplatin dose ≥ 100 mg/m² in 13% of those randomised.

Four patients were alcohol abusers. A perfect balance of input variables between treatment groups was achieved by the central randomisation procedure. The proportion of patients receiving single-day chemotherapy or single-day cisplatin therapy, as well as other variables, was also well balanced (Table 2).

Table 3 summarises the results for larger treatment groups (factorial design). Figures 2 and 3 show the subgroup percentages of complete and partial response for Day 1 and Days 1–6 respectively. Patients receiving dexamethasone showed a significantly improved response (p = 0.02 and p = 0.0004) for both primary efficacy variables: complete response for Day 1 improved from 66% (CI: 60%–73%) to 76% (CI: 28%–40%) to 50% (CI: 44%–57%).

Table 3. Complete response rates for Day 1 and Days 1–6 of randomised patients, separated by chemotherapy fractionation status, both for any chemotherapy agent and for cisplatin

Chemotherapy selection	Reference period	Navoban® (tropisetron) 5 mg	Navoban® (tropisetron) 10 mg	No alizapride	Alizapride	No DXM	DXM
All chemotherapy		*n* = 221	*n* = 224	*n* = 220	*n* = 220	*n* = 225	*n* = 220
	Day 1	158 (71%)	161 (72%)	154 (68%)	165 (75%)	150 (67%)	169 (76%)
	Days 1–6	88 (40%)	99 (44%)	84 (37%)	103 (47%)	76 (34%)	111 (50%)
Unfractionated		*n* = 142	*n* = 150	*n* = 150	*n* = 142	*n* = 148	*n* = 144
	Day 1	92 (65%)	97 (65%)	94 (63%)	95 (67%)	85 (57%)	104 (72%)
	Days 1–6	57 (40%)	60 (40%)	52 (35%)	65 (46%)	44 (30%)	73 (51%)
Fractionated		*n* = 79	*n* = 74	*n* = 75	*n* = 78	*n* = 77	*n* = 76
	Day 1	66 (84%)	64 (86%)	60 (80%)	70 (90%)	65 (84%)	65 (86%)
	Days 1–6	31 (39%)	39 (53%)	32 (43%)	38 (49%)	32 (42%)	38 (50%)
No CDDP		*n* = 163	*n* = 176	*n* = 167	*n* = 172	*n* = 172	*n* = 167
	Day 1	107 (66%)	126 (72%)	108 (65%)	125 (73%)	109 (63%)	124 (74%)
	Days 1–6	70 (43%)	84 (48%)	69 (41%)	85 (49%)	64 (37%)	90 (54%)
Single day CDDP		*n* = 24	*n* = 23	*n* = 28	*n* = 19	*n* = 24	*n* = 23
	Day 1	20 (83%)	13 (57%)	21 (75%)	12 (63%)	15 (63%)	18 (78%)
	Days 1–6	11 (46%)	6 (26%)	8 (29%)	9 (47%)	6 (25%)	11 (48%)
Mult. day CDDP		*n* = 34	*n* = 25	*n* = 30	*n* = 29	*n* = 29	*n* = 30
	Day 1	31 (91%)	22 (88%)	25 (83%)	28 (97%)	26 (90%)	27 (90%)
	Days 1–6	7 (21%)	9 (36%)	7 (23%)	9 (31%)	6 (21%)	10 (33%)

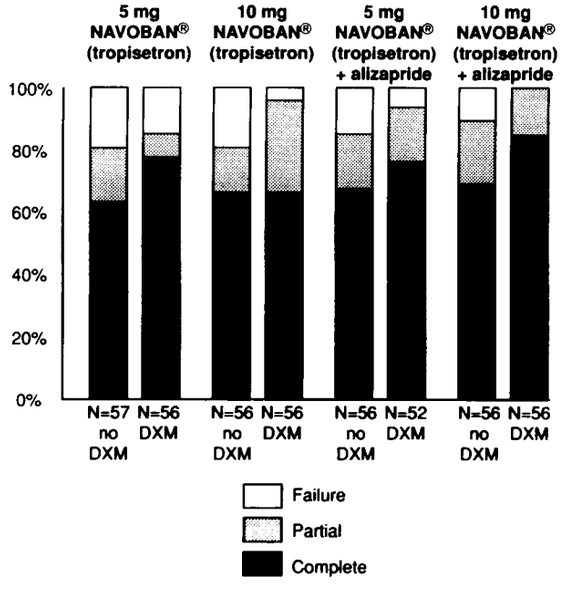

Figure 2. Response Day 1 of Course 2 for randomised patients: trop. = Navoban® (tropisetron).

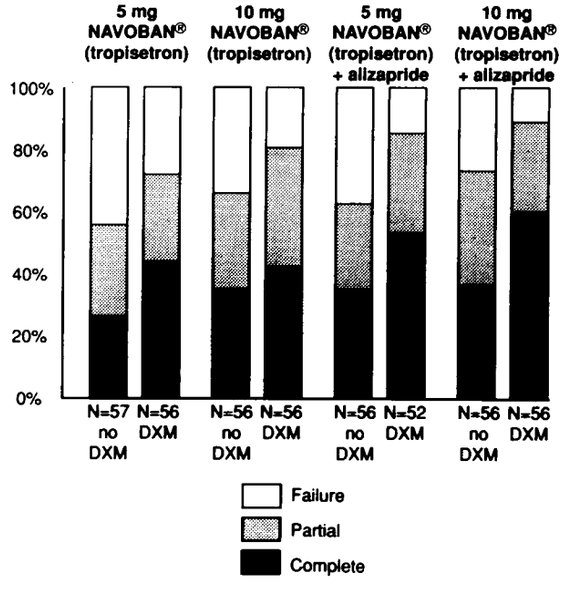

Figure 3. Response Days 1–6 of Course 2 for randomised patients: trop. = Navoban® (tropisetron).

Table 4. Adverse events reported in over 1% of patients randomised

Adverse event	Navoban® (tropisetron) 5 mg (*n* = 221)	Navoban® (tropisetron) 10 mg (*n* = 224)	No alizapride (*n* = 225)	Alizapride (*n* = 220)	No DXM (*n* = 225)	DXM (*n* = 220)
Constipation	27 (12%)	21 (9%)	23 (10%)	25 (11%)	24 (11%)	24 (11%)
Headache	21 (10%)	15 (7%)	18 (8%)	18 (8%)	18 (8%)	18 (8%)
Fatigue	10 (5%)	9 (4%)	15 (7%)	4 (2%)	7 (3%)	12 (5%)
Epigastric pain	6 (3%)	8 (4%)	7 (3%)	7 (3%)	3 (1%)	11 (5%)
Pyrosis	7 (3%)	6 (3%)	8 (4%)	5 (2%)	2 (1%)	11 (5%)
Diarrhoea	8 (4%)	3 (1%)	6 (3%)	5 (2%)	6 (3%)	5 (2%)
Dizziness	4 (2%)	6 (3%)	6 (3%)	4 (2%)	4 (2%)	6 (3%)
Hiccups	5 (2%)	4 (2%)	3 (1%)	6 (3%)	4 (2%)	5 (2%)
Fever	5 (2%)	2 (1%)	5 (2%)	2 (1%)	5 (2%)	2 (1%)
Abdominal pain	3 (1%)	4 (2%)	3 (1%)	4 (2%)	3 (1%)	4 (2%)

The addition of alizapride ($p = 0.14$ and $p = 0.041$), unlike dexamethasone, improved the primary outcome variables, from 68% (CI: 62%–74%) to 75% (CI: 40%–54%) for Days 1–6. Complete response rates were not altered when the dose of Navoban® was doubled ($p = 1$ and $p = 0.37$), although on Days 1–6 fewer treatment failures were noted with the higher dose (22% vs. 32%).

We assessed the uniformity of the effects of the three treatments by comparing their effects in subgroups which were defined by fractionation of any chemotherapy and of cisplatin (Table 3). This study was not designed to test hypotheses based on these smaller subgroups, so these comparisons are merely descriptive and should be used only to generate further hypotheses. The improvement in complete response rate associated with dexamethasone was almost wholly confined to single-day chemotherapy regimens; this was the only striking result in the exploratory analysis.

The power to test for treatment interactions was not provided by the sample size used in this study. No such interactions were suggested by our data; for example, the overall effect of adding alizapride was also present when we considered only those patients receiving Navoban® plus dexamethasone. Complete response rates for 108 patients receiving all three antiemetic agents and for 112 receiving Navoban® plus dexamethasone were 81% vs. 72% for Day 1 and 57% vs. 44% for Days 1–6.

Thirty-six patients died either during or within one month after the study – although none of the deaths were believed to be connected with the drugs used in the study. Constipation (13%) and headache (8%) were the most frequently observed adverse events and, for the randomised patients, most of these reactions were spread over the various treatment groups – apart from epigastric pain and pyrosis, which occurred mainly in patients treated with dexamethasone. Table 4 lists all adverse events observed in at least 1% of the randomised patients.

Discussion

There are no well standardised criteria for the evaluation of nausea and emesis associated with cytotoxic chemotherapy administration. Nausea is the main determinant of low complete response rates. It is difficult to grade nausea, and only its complete absence is well defined. The primary end-point must therefore be complete absence of nausea and vomiting. The quest continues for additional treatments such as combination therapies of serotonin antagonists and other agents (i.e. corticosteroids, dopamine D_2-antagonists and benzodiazepines), because complete elimination of nausea and vomiting is still not achievable in all patients receiving chemotherapy. Combinations based on metoclopramide are currently yielding to combinations with the more effective 5-HT_3-antagonists for chemotherapy containing cisplatin.[11] Our ultimate goal remains unaltered: complete elimination of both acute and delayed nausea and emesis.

The lowest complete response rates are often, with current antiemetic treatment, noted after Day 1. This delayed reaction is similarly characteristic of unfractionated chemotherapy regimens and offers scope for improvement. It is not altogether surprising that the observed additional effects on complete response

rates in this study were more significant for the Days 1–6 period than for Day 1, and even more pronounced in the subgroup of patients on single-day chemotherapy.

We were able to randomise an adequate number of patients to detect a 15% improvement in complete response rate, using somewhat broad criteria of eligibility. Our results were similar to those of other trials combining 5-HT_3-antagonists, trials which involved smaller but more homogeneous patient populations. Bregni *et al.*,[12] for instance, treated 58 patients (on cyclophosphamide and melphalan) in an open-label comparison of Navoban® with a combination of this compound and the D_2-antagonist haloperidol. Their findings indicate that the combination worked better than Navoban® on its own in reducing the number of vomiting episodes during the 3-day study period. Similarly, Herrstedt *et al.*[13] used a randomised, double-blind, cross-over trial to assess the efficacy of a combination of ondansetron (a serotonin-antagonist) and metopimazine (a dopamine D_2-antagonist) in 30 breast cancer patients showing an incomplete response to Zofran® (ondansetron) on the previous course. During the previous course, the response rate had been incomplete for all patients. In 10 out of 30 treatments with Zofran® plus metopimazine, however, no nausea was noted for the entire treatment period, in contrast to 4 out of 30 for Zofran® alone.

While we still do not fully understand the precise antiemetic mechanism of the corticosteroids, their ability to enhance the efficacy of metoclopramide and the 5-HT_3-antagonists is now well known.[6,11] Our own results support those of Schmidt *et al.*,[5] who reported complete control of nausea and vomiting over the entire 6-day assessment period in a significant proportion (39%) of 160 chemotherapy-naive carcinoma patients with a Navoban®/dexamethasone combination following cisplatin. Several other studies[14–18] have confirmed how the action of the 5-HT_3-antagonists can be enhanced with corticosteroids – notably with dexamethasone, the best studied of this class of drugs.

We have, at present, no information on the additional effect of substituted benzamides in conventional doses, and in their role of D_2-receptor antagonists, on the antiemetic potency of serotinin antagonists. Our own study was not able to show any noticeable improvement, although it is generally acknowledged that a combination of all three agents can rescue some specific patients.

To sum up, 1072 patients treated with Navoban® 5 mg once daily during a first course of emetogenic chemotherapy showed a complete response, with no nausea or emesis in 72% for Day 1, 61% for Day 2 and 48% for Days 1–6. We tried to identify the best additional antiemetic treatment for those patients who had experienced an incomplete response on any day of Course 1, and this we did by using a 2 x 2 x 2 factorial study design for Course 2.

For Day 1 and Days 1–6 of Course 2, a significant increase in complete response rate was observed for the addition of dexamethasone each day of the course. When dexamethasone was added to Navoban® during Course 2, some half of the incomplete responders of Course 1 remained free from nausea and vomiting. The effect of adding this compound was most noticeable on single-day chemotherapy courses; alizapride had a less significant effect, although this improved for the Days 1–6 response. The current dose recommendation is supported by the fact that doubling the dose of Navoban® from 5 mg to 10 mg once daily did not significantly alter complete response rates.

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