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Research paper

Tropisetron in the prevention of acute and delayed nausea and vomiting over six courses of emetogenic chemotherapy

H Bleiberg, F Hulstaert,[1] M Buyse[2] and P De Keyser[1]
Unité de Gastroenterologie, Institut Jules Bordet, rue Héger-Bordet 1, 1000 Brussels, Belgium.
Tel: (+32) 2 535 35 67; Fax: (+32) 2 538 08 58. [1]Sandoz Phamra, Chaussée de Haecht 226, 1030 Brussels, Belgium. [2]International Institute for Drug Development, Brussels, Belgium.

Tropisetron (Navoban®) suppresses nausea and vomiting induced by cancer chemotherapy by antagonizing central and peripheral 5-HT_3 receptors. In this open-label study, tropisetron was evaluated in 873 patients who were either refractory to antiemetic treatment during previous chemotherapy or at high risk of emesis as a result of current chemotherapy. The most commonly used agents alone or in combination were cyclophosphamide (35%), fluorouracil (30%), carboplatin (24%) and cisplatin (21%). The primary tumors were breast cancer (27%), lung cancer (16%), gynecological cancers (12%) and lymphoma (9%). Tropisetron was administered as a 15 min infusion prior to chemotherapy and an additional oral 5 mg dose was taken by 80% of the patients on subsequent days. During course 1, complete response to tropisetron was obtained in 64% of patients on day 1, 54% on day 2, 63% on day 3, 71% on day 4 and 77% on day 5. Very similar response rates were found for the six chemotherapy courses. There were few failures after complete and partial response, at maximum 3 and 15%, respectively. Moreover, 24–38% of those with partial response and 7–29% of those with failure could achieve a complete response during the following cycle. The treatment was well tolerated, the most frequently reported adverse events being constipation (3.7%) and headache (2.6%).

Key words: Antiemetics, cancer, nausea, serotonin antagonists, tropisetron, vomiting.

Introduction

Control of emesis has made major progress thanks to the use of 5-HT_3 receptor antagonists (5-HT_3-RA). In the vast majority of the studies investigating the activity of a 5-HT_3-RA antiemetic therapy, the antiemetic agent was given in order to control emesis induced by the most emetogenic agents, frequently cisplatin.

Very little information is available regarding the activity of a 5-HT_3-RA overall, for a broad range of chemotherapies and durations of treatment. Our purpose was to investigate the long-term digestive tolerance of chemotherapy when given with a 5-HT_3-RA.

Tropisetron (Navoban®; Sandoz Pharma, Basle, Switzerland) is a selective competitive antagonist of the 5-HT_3 receptor. Administration of a single daily dose of 5 mg tropisetron proved to be highly effective and well tolerated in the prevention of chemotherapy-induced nausea and vomiting in adults.[1] The aim of the present open-label study was to confirm the reported efficacy and safety of tropisetron in the prevention of nausea and vomiting using a large and diverse group of patients treated with various emetogenic chemotherapies during the acute and delayed phases of emesis of consecutive cycles of chemotherapy. An interim analysis has already been published on the response observed the first day of two consecutive cycles in 545 patients.[2] The current report, based on 873 patients, describes the activity of Navoban from days 1 to 5 during consecutive chemotherapy courses.

Patients and methods

Patients

This is a prospective, multicentric, uncontrolled, open-label study initiated in 1988 when no 5HT_3-RA were commercialized. The study was started as a compassionate use program for patients previously

Navoban® was supplied by Sandoz Pharma Ltd (Basle, Switzerland).

Correspondence to H Bleiberg

treated by chemotherapy and who had been refractory to non-5-HT_3-RA antiemetic treatment. Due to the lack of effective antiemetic treatment at that time, patients who, in the opinion of the investigator, were at high risk of severe emesis as a result of current chemotherapy were also accepted. All chemotherapeutic agents alone or in combination, and of various emetogenic potentials, were acceptable. They were administered either as an i.v. bolus or by continuous infusion, for one or more days. Chemotherapeutic agents were graded according to their emetogenic potential from 1 (lowest potential) to 5 (highest potential) as described before.[2] Patients with advanced hepatic, renal or heart failure, uncontrolled infection, or childbearing potential without effective contraception were excluded. The study respected the guidelines as laid down by the Declaration of Helsinki and its amendments concerning medical research in humans.

Treatment

Initially tropisetron was used at a once-daily dose of 5 or 10 mg. A once-daily dose of tropisetron 5 mg was later recommended based on the results of dose-comparative studies.[3] Tropisetron was administered slowly i.v. over at least 1 min (undiluted or diluted in normal saline) before the start of chemotherapy on day 1 and i.v. or by mouth on the subsequent days of each course. Tropisetron was taken by mouth as a single morning dose, 1 h before food intake.

Assessment of activity

The primary outcome of interest was the response to tropisetron on day 1 and days 1–5 of each chemotherapy course. The efficacy of tropisetron was assessed using a grading scale based on the combined measure of both nausea and vomiting. The response to tropisetron per 24 h periods on the first 5 days of each chemotherapy course was graded as complete (no nausea nor vomiting), partial (one to four vomits and/or less than 5 h of nausea) or failure (more than four vomits and/or at least 5 h of nausea). No attempt was made to assess the severity of nausea. The first 24 h period is referred to as day 1 of the course. Efficacy and safety results were obtained from the patient as well as from the nursing staff and recorded on case report forms by the investigator.

Statistics

Given the open and uncontrolled nature of this study, all statistics are descriptive. For the purpose of statistical analysis efficacy results are reported separately for the first six courses of each patient and for all courses grouped. Antiemetic response for course 1 was analyzed by sex, age, tumor type, chemotherapy fractionation and combination of chemotherapy agents. Patients who received single-day cisplatin chemotherapy were also considered separately with results for course 1 analyzed by cisplatin dose. We also analyzed whether the antiemetic response to a course of chemotherapy could be predicted based on the response seen in the course preceding it.

Results

The study was conducted between October 1988 and January 1994 in 47 centers in Belgium. We reported the results of a total of 873 patients for which information for at least one course is available. The 3096 chemotherapy courses for which there is information on the activity on day 1 were included in the efficacy analysis. These involved 869 patients in course 1, 604 in course 2, 440 in course 3, 323 in course 4, 230 in course 5 and 166 in course 6. The other courses were only included in the overall description.

The majority of the patients were female (60%). The median age was 54 years (range 18–84). The most frequent diagnosis was breast cancer (27%) followed by lung cancer (16%), ovarian cancer (12%) and lymphoma (9%). Most patients had been previously treated with chemotherapy (71%), more than half had received previous antiemetic treatment (66%). Most antiemetic treatments were non-5-HT_3-RA (alizapride, metoclopramide and lorazepam). Only 10% of the patients had received the 5-HT_3-RA ondansetron.

Thirty percent of the patients had data for only one chemotherapy course and 86% for one to six courses. Chemotherapy agents were given in combination in 764 patients (88%) during the first course of the study and this fraction decreased gradually to 137 patients (83%) for course 6. In 63% of the courses, the chemotherapy was administered on a single day varying from 55% for course 1 to 70% for course 6. The most commonly used chemotherapy agents were cyclophosphamide (35%), fluorouracil (30%), carboplatin (24%), cisplatin (21%), doxorubicin (18%), epirubicin (16%), methotrexate (14%), etoposide (15%) and mitoxantrone (11%). Other agents were

used in less than 10% of the courses. The types of agents were quite similar across the courses.

All 873 patients received tropisetron during one (30%) or more courses of emetogenic chemotherapy or 3149 courses overall. A decreasing number of patients received tropisetron over multiple courses resulting in 615 course 2 results, 449 course 3 results, 332 course 4 results, 233 course 5 results and 168 course 6 results. A total of 110 patients (13%) received tropisetron for more than six courses. During course 1, tropisetron was administered for a median duration of 5 days, ranging from a single day in 22% of the patients to 7 days or more in 17% of the patients. These percentages were consistent across the six courses.

The great majority of the patients (93%) received no other antiemetic agent besides tropisetron during course 1 and the following courses. Corticosteroids were part of chemotherapy in 3% of the patients or were added as an antiemetic agent in another 3% of the patients. In 1% of the patients, alizapride was added to tropisetron. Lorazepam, prochlorperazine, dexchlorpheniramine, chlorpromazine, metoclopramide and metopimazine were all used in less than 1% of the cases.

Complete response on day 1 (absence of both nausea and vomiting) was observed in 64% of the patients for course 1 and in 66% of the patients for course 2. This percentage decreased to 57% for course 6 (Table 1). For all six courses the percentage of complete responders was the lowest on day 2 (50-70%) and increased on the subsequent days. The response pattern was quite similar over the six courses, and between 38 and 45% of the patients remained completely free of both nausea and vomiting during the 5 day observation period. A complete or partial response for days 1-5 was observed in 85-87% for the various courses.

Complete response rates both for day 1 and for days 1-5 were lower in females (61 and 40%) than in men (70 and 43%). Breast cancer, accounting for 27% of the primary tumor types, accounted for 44% of the antiemetic treatment failures on day 1. Response rates did not seem to vary with respect to patients age.

In the predominantly pretreated, refractory patients population, chemotherapy agents alone or in combination did not help predicting the response. Only the higher doses of cisplatin had a slightly poorer control of emesis as compared to lower doses of cisplatin and to other agents (Figure 1). Even by fractionating chemotherapy the complete response rate was only slightly higher: 67% for fractionated chemotherapy versus 61% for non-fractionated chemotherapy.

Table 2 shows the response on day 1 of courses 2-6 according to the response obtained in the previous course. Among the patients who had a complete response in any cycle, 80% still had an opportunity of having a complete response during the following cycle. Between 15 and 18% had a partial response and only 2-3% had a failure. Among the patients who had a partial response, 50-67% will again have a partial response, while 24-38% achieved a complete response during the following cycle and only 5-15% had a failure. Among the patients who failed during a previous cycle, 7-29% showed a complete response,

Table 1. Antiemetic response to tropisetron over six chemotherapy courses and over 5 days during each course (percentages)

	Response	Course 1 (*N*=869)	Course 2 (*N*=604)	Course 3 (*N*=440)	Course 4 (*N*=323)	Course 5 (*N*=230)	Course 6 (*N*=166)
Day 1	complete	64	66	62	61	58	57
	partial	29	27	30	31	33	36
	failure	7	7	9	7	8	7
Day 2	complete	54	57	52	53	50	51
	partial	36	33	38	39	40	42
	failure	10	9	9	8	10	7
Day 3	complete	63	63	62	63	63	60
	partial	31	29	31	29	33	35
	failure	6	7	7	7	3	4
Day 4	complete	71	71	70	68	73	69
	partial	22	23	22	24	22	25
	failure	3	3	6	5	3	4
Day 5	complete	77	77	77	73	78	75
	partial	16	17	17	21	17	19
	failure	2	2	4	2	2	2
Worst	complete	41	45	40	40	39	38
	partial	46	42	45	46	47	49
	failure	13	13	15	13	14	13

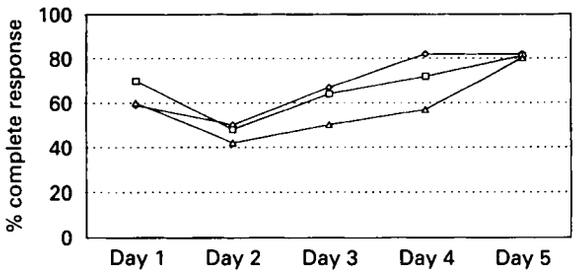

Figure 1. Complete response for nausea and vomiting over 5 days during first course of tropisetron by cisplatin dose (mg/m^2) in patients receiving single day cisplatin chemotherapy: ◊, <65 mg (*N*=38); □, 65–85 mg (*N*=64); △, >85 mg (*N*=45).

Table 2. Day 1 response in the further course in relation to the response obtained in the previous course (percentages)

Further course		Response in previous course		
		Complete	Partial	Failure
Course 2	complete	81	38	29
	partial	17	50	35
	failure	2	12	35
Course 3	complete	82	24	11
	partial	16	61	37
	failure	2	15	52
Course 4	complete	85	24	28
	partial	15	64	24
	failure	0	12	48
Course 5	complete	77	33	7
	partial	20	59	29
	failure	3	8	64
Course 6	complete	79	28	9
	partial	18	67	36
	failure	3	5	54

24–37% a partial response while 35–54% again had a failure.

Constipation was the most frequently reported adverse event overall (in 3.7% of the patients), followed by headache (2.6%), abdominal pain (0.6%) and gastric pain (0.5%). Fever, diarrhea, erythema and dizziness were reported for less than 0.5% of the patients. Four patients died while on study. None of these deaths were considered related to the study drug by the investigators.

Discussion

This large compassionate use program was started before any other 5-HT$_3$-RA was commercialized. We wanted to evaluate the activity of a 5-HT$_3$-RA, i.e. tropisetron, in patients refractory to previous non-5-HT$_3$-RA and/or at high risk of emesis. In this descriptive non-randomized study, it was felt that the high number of patients treated, the wide variety of chemotherapy regimens as well as the long-term use of the antiemetic treatment during successive cycles would give a realistic understanding of the impact of 5-HT$_3$-RA treatment on a daily clinical basis.

The complete response rate of 64% obtained on the whole population, whatever the chemotherapy given, is in the range of what we would expect with any 5-HT$_3$-RA. However, data involving a similar population of refractory patients and such a variety of chemotherapy regimens do not exist.

For registration purposes, most of the studies focused on the use of cisplatin, which is considered as the most emetogenic agent. It is generally assumed that less emetogenic agents would respond at least as well. Even in our patient population receiving single-day cisplatin-containing regimens, total control of emesis on day 1 varies from 60 to 70% (Figure 1). For doses lower than 85 mg/m^2 (cut-off points were arbitrarily selected), the control of emesis from days 1 to 5 is comparable to what is observed with less emetogenic chemotherapy. However, at doses higher than 85 mg/m^2, complete control is slightly lower, about 40% on day 2 when symptoms are generally the worst. This level of complete control is in the range of what is usually observed with other 5-HT$_3$-RA in patients receiving high-dose cisplatin.[4,5]

The type of chemotherapy plays an important role in the incidence and severity of nausea and vomiting in patients receiving their first course of chemotherapy. In our series, one could be surprised by the lack of difference in the control of emesis for chemotherapy known to have different emetogenic potentials. This might be due to the fact that for patients previously treated and who had already experienced emesis, the gastrointestinal symptoms following further chemotherapy administration were probably related to other factors, probably mostly psychogenic, rather than the emotogenic stimulus of the chemotherapeutic agent. In that population, the type of chemotherapy loses its prognostic relevance and patients tend to behave similarly regardless of the type of chemotherapy administered.

During consecutive cycles the number of patients is decreasing due to progression of the disease, anticancer treatment modification and death. However, it cannot be totally excluded that some patients went off study because of antiemetic treatment failure. Consecutive administration of tropisetron indicates that the control of emesis remains quite acceptable. There

were very few failures after complete and partial response, between 3 and 15%, respectively. Moreover, 24-38% of those with partial response and 7-29% of those with failure could achieve a complete response during the following cycle. This shift towards a better control of emesis during consecutive cycles in a population where the majority of patients are refractory to antiemetic treatment might be explained by the fact that the severity of the symptoms was lessened. Patients were therefore less anxious during the following cycles and had improved control of their symptoms.

Conclusion

This large prospective compassionate study shows that tropisetron used as a single agent at the dose of 5 mg i.v. before chemotherapy and orally during the following days can effectively reduce the incidence of chemotherapy-induced nausea and vomiting. This effect is reproducible during successive cycles and our data suggest that, in the long run, the severity of the symptoms can even decrease.

Acknowledgments

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