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Tropisetron plus Haloperidol to Ameliorate Nausea and Vomiting Associated with High-dose Alkylating Agent Cancer Chemotherapy

Marco Bregni, Salvatore Siena, Massimo Di Nicola, Gianni Bonadonna and Alessandro M. Gianni

Tropisetron is a novel antiserotoninergic drug with potent and specific activity against cancer chemotherapy-induced emesis. High-dose cyclophosphamide or high-dose melphalan are chemotherapeutic regimens associated with severe nausea and vomiting refractory to current antiemetic medications. We compared in a randomised open label study the antiemetic efficacy of tropisetron and alizapride in a first group of 32 consecutive patients treated with high-dose alkylating agent chemotherapy with or without autologous bone marrow transplantation. Tropisetron was more effective than alizapride in reducing vomiting episodes. In the first 24 h of treatment the median number of episodes in patients treated with tropisetron was 5 compared with 9 episodes in the alizapride group ($P = 0.005$). In the 72 h study period the median number of emetic episodes was 6 in the tropisetron group and 12 in the alizapride group ($P = 0.004$). In a second group of 26 consecutive patients, a combination of tropisetron plus haloperidol, a dopamine antagonist, was employed for prevention of emesis. This combination was more effective than tropisetron as single agent in preventing emetic episodes, as the median number of emetic episodes in the 72 h of observation was only 3, while they were 6 in the tropisetron group. The side-effects of tropisetron were mild and reversible upon discontinuation of the drug. We conclude that tropisetron is an effective antiemetic drug when employed in high-dose alkylating agent chemotherapy, and that its activity is potentiated by the association with haloperidol.
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INTRODUCTION

NAUSEA AND VOMITING are side-effects associated with cancer chemotherapy [1]. Vomiting may produce malaise, dehydration and electrolyte imbalance. The diminished quality of life induced by vomiting may lead to a refusal of anticancer therapy or to reduced compliance for medications. Current medications for prevention of vomiting are effective against strongly emetogenic drugs but are not devoid of side-effects, particularly in younger patients [1]. In recent years there has been considerable interest in increasing dose and/or dose intensity of cancer chemotherapy [2], and notably this increase has been associated with increase of severity and frequency of vomiting. Our group has been exploring the effectiveness and the toxicity of a sequential high-dose chemotherapy regimen employing high-dose cyclophosphamide and high-dose melphalan in patients with stage II breast cancer at high risk of relapse or with high-grade diffuse non-Hodgkin lymphoma [3]. Both chemotherapeutic agents induce severe vomiting which is only partially ameliorated by current antiemetic regimens, including continuous intravenous

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infusion of prochloperazine or intravenous administration of substituted benzamides [4].

Recently, potent and specific antiemetic drugs acting by blocking the serotonin-3 receptor have been introduced in the clinical practice. These drugs are highly effective in preventing nausea and vomiting induced by cisplatin and other emetogenic chemotherapeutic agents [5]. One of these drugs, tropisetron, was studied in 10 patients undergoing multiple cycles of cisplatin-containing chemotherapy, and completely prevented vomiting in 66% of the cases [6]. Based on these promising results, we compared in a randomised open label study the safety and efficacy of tropisetron vs. alizapride in prevention of nausea and vomiting induced by cyclophosphamide or melphalan. Moreover, we investigated in a group of similarly treated patients if the therapeutic efficacy of tropisetron could be increased by association with scopolamine, an anticholinergic drug, and/or haloperidol, a selective dopamine receptor antagonist.

PATIENTS AND METHODS

Study design

32 patients were enrolled in a randomised open label study to compare the efficacy and the safety of tropisetron or alizapride in preventing nausea and vomiting induced by high-dose alkylating agent chemotherapy. After completion of this study, a group of 26 consecutive patients treated at our institution with high-dose alkylating agents received tropisetron plus haloperidol with or without scopolamine for prevention of nausea and vomiting. The studies were approved by the Institute's Committee for Clinical Investigations, and patients gave informed oral consent.

Patients

Eligible patients were older than 18 and younger than 60 years, had a histologically confirmed diagnosis of malignancy, a Karnofsky performance status ≥ 70, and normal cardiac, hepatic, renal and pulmonary functions. Patients included in this study were: 43 patients with surgically resected stage II breast cancer with 10 or more metastatic axillary nodes, 4 patients with Hodgkin's disease either refractory to or relapsed within 12 months after first-line chemotherapy, 8 patients with diffuse high-grade non-Hodgkin lymphoma at disease presentation, and 3 patients with diffuse high-grade non-Hodgkin lymphoma refractory to first-line chemotherapy. All patients were previously untreated with cancer chemotherapy, except patients with Hodgkin's disease who had been treated with 6–8 cycles of alternating mechlorethamine/vincristine/procarbazine/prednisone–doxorubicin/bleomycin/vinblastine/decarbazine (MOPP/ABVD) chemotherapy [7], and patients with refractory non-Hodgkin lymphoma who had been treated with methotrexate/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin/cotrimoxazole (MACOP-B) chemotherapy program [8].

Chemotherapy

Emetogenic high-dose chemotherapy treatments utilised in this study were: (i) cyclophosphamide, 7 g/m^2 in five 1 h injections over 13 h. For urothelial protection, patients were given intravenous bolus mesna every 3 h for 12 doses. Starting 24 h after the initiation of cyclophosphamide, patients received recombinant human granulocyte–macrophage colony stimulating factor (rhuGM-CSF) (mammalian, glycosilated, Sandoz/Schering-Plough) at dosages of 5–11 μg protein per kg body weight per day for 14 days, by intravenous or subcutaneous administration. Neither mesna nor rhuGM-CSF are emetogenetic. (ii) melphalan, 200 mg/m^2 in three intravenous bolus injections over 6 h. 24 h later bone marrow and peripheral blood haematopoietic progenitor cells, previously collected and cryopreserved, were thawed and rapidly infused intravenously over 30 min. Meperidine, 50 mg in 50 ml normal saline was administered in 30 min immediately before reinfusion to avoid chills due to infusion of thawed cellular material.

The overall treatment program for patients with breast cancer consisted of the following drugs: cyclophosphamide, 7 g/m^2 on day 0; vincristine, 1.4 mg/m^2 and methotrexate, 8 g/m^2 plus leucovorin rescue approximately on day 17; cisplatin, 60 mg/m^2 on day 23 and 30; melphalan, 200 mg/m^2 approximately on day 40; reinfusion of autologous haematopoietic progenitor cells on day 41 [9]. Patients with non-Hodgkin lymphoma and Hodgkin's disease received the same treatment with high-dose etoposide, 2 g/m^2 instead of cisplatin and with the addition of fractionated total body irradiation (TBI) 10–12.5 Gy to melphalan, 120–140 mg/m^2 [10]. Patients receiving TBI plus melphalan were not evaluated in this study. Treatment with high-dose alkylating agents was administered on inpatient basis in single-bed rooms of the Bone Marrow Transplant Unit of the National Tumour Institute. During the study period patients received acetazolamide and allopurinol orally for ensuring an adequate urinary flow and for prevention of urate nefropathy. Patients did not receive antiemetic treatments other than those detailed below.

Antiemetic treatment

Patients enrolled in the randomised study were assigned to receive tropisetron or alizapride according to a computer-generated randomisation scheme supplied by Sandoz SpA (Milan, Italy).

Tropisetron (Sandoz SpA) 10 mg diluted in 100 ml of normal saline, was administered intravenously in 15 min starting 30 min before the initiation of chemotherapy, then orally at the dose of 5 mg at 6 and 12 h, and at the same dosage every 12 h for 4 additional doses. Alizapride (Vita Farmaceutici, Italy) 200 mg was administered intravenously every 6 h starting 30 min before the initiation of chemotherapy for the first 24 h, and orally at the dose of 50 mg every 6 h during the next 48 h [11].

After completion of the randomised study, a second group of patients was treated with tropisetron at the same dosages and with the same schedule as described above, and also received haloperidol (Lusofarmaco, Italy) 0.5 mg orally every 12 h concurrently with the administration of tropisetron. 12 patients in this latter group also received scopolamine (Recordati, Italy) 1.5 mg transdermally starting 12 h before chemotherapy to 72 h thereafter.

Evaluation of response

Patients were continuously observed for 72 h by experienced staff members starting on the day of chemotherapy. Number, volume and severity of emetic episodes were recorded every 2 h. Nausea was assessed every 2 h according to a 0–3 arbitrary numeric scale (0 = absent, 1 = minor, 2 = moderate, 3 = severe). Side-effects were recorded and the opportunity of withdrawing or reducing dosage of antiemetic treatment was evaluated.

The Mann–Whitney rank-sum test was utilised to evaluate differences among treatment groups in the number of emetic episodes, time to the first emetic episode and severity of nausea.

RESULTS

The characteristics of the patients participating in this study are shown in Table 1. The majority of treatments (43 out of

Table 1. Characteristics of patients

	All treatments	Treatment group		
		Alizapride	Tropisetron	Tropisetron plus haloperidol
No. of treatments	58	17	15	26
Age				
Median	42	46	46	39
Range	22–54	26–52	26–54	22–52
Disease				
Breast cancer	43	16	13	14
NHL	11	—	1	10
Hodgkin's	4	1	1	2
Previous treatment				
MOPP/ABVD	4	1	1	2
MACOP-B	4	—	1	3
Present chemotherapy				
High-dose cyclophosphamide	39	8	10	21
High-dose melphalan	19	9	5	5

NHL = Non-Hodgkin lymphoma.

58) were administered to chemotherapy-naive patients with surgically resected breast cancer with more than 10 positive axillary nodes, who were receiving high-dose alkylating agent chemotherapy in an adjuvant setting [9]. Patients enrolled in the randomised study comparing alizapride to tropisetron were well balanced as far as age, disease, and previous treatment were concerned (Table 1).

The results of the randomised study suggested that tropisetron was more effective than alizapride in reducing nausea and the number of vomiting episodes (Table 2). In the first 24 h of

Table 2. Alizapride vs. tropisetron

	Alizapride	Tropisetron	P†
Emetic episodes in initial 24 h	(%)	(%)	
0	1 (6)	2 (13)	
1–5	4 (23)	9 (60)	
>5	12 (71)	4 (27)	
Median	9	5	0.005
Range	0–31	0–12	
Emetic episodes in study period (%)			
0	0	2 (13)	
1–5	3 (17)	5 (34)	
>5	14 (83)	8 (53)	
Median	12	6	0.004
Range	4–40	0–23	
Latency (hours from therapy)			
Median	65	13	
Range	2–24	8–28	0.001
Grade of nausea*			
Median	2	1	
Range	0–3	0–3	0.061

*0–3 arbitrary scale.
†Mann–Whitney rank sum test.

Table 3. Tropisetron plus haloperidol

	No. of emetic episodes (%)	
	Initial 24 h	Study period
0 episodes	6 (23)	6 (23)
1–5 episodes	15 (57)	13 (50)
>5 episodes	5 (20)	7 (27)
Median	2	3
Range	0–8	0–10

treatment 2 patients in the tropisetron group (13%) and 1 patient in the alizapride group (6%) enjoyed complete protection from nausea and vomiting. In the same study period, 73% of patients treated with tropisetron and 31% of alizapride patients reported 5 or fewer vomiting episodes. The median number of episodes in patients treated with tropisetron was 5, compared with 9 episodes in the alizapride group ($P = 0.005$). In the 72 h study period, 2 patients in the tropisetron group (13%) and no patient in the alizapride group reported a complete protection from vomiting episodes (not statistically significant), while 47% of tropisetron patients and 17% of alizapride patients had 5 or fewer vomiting episodes. In the same study period the median number of emetic episodes was 6 in the tropisetron group, and 12 in the alizapride group ($P = 0.004$). The median interval of time from initiation of therapy to the first emetic episode (latency) was longer in the tropisetron group (13 h) than in the alizapride group (6.5 h; $P = 0.001$). Nausea was present in both treatment arms, and also if the median grade of nausea was minor in the tropisetron group (grade 1) and moderate in the alizapride group (grade 2), this difference did not reach statistical significance ($P = 0.061$). There was no difference in the results of antiemetic treatment as far as previous chemotherapy was concerned.

Prompted by these initial observations, we then evaluated whether the addition of an antidopaminergic agent to the serotonin receptor blockade accomplished by tropisetron could further increase the control of vomiting. Thus a second group of 26 consecutive patients treated with high-dose alkylating agent chemotherapy at our institution received a combination of tropisetron plus haloperidol for prevention of vomiting. These patients were younger than the patients entered in the randomised study (39 vs. 46 years; Table 1), and 5 out of 26 were pretreated with full dose cancer chemotherapy (MOPP/ABVD or MACOP-B). The combination of tropisetron plus haloperidol was effective in the control of nausea and vomiting caused by high-dose alkylating agents. 6 patients (23%) reported no vomiting episodes in the initial 24 h and in the 72 h study period (Table 3). 80% and 73% of patients treated with the combination had equal or less than 5 vomiting episodes in the 24 and in the 72 h study period, respectively. The median number of emetic episodes was 2 (range 0–8) in the initial 24 h, and 3 (range 0–10) in the 72 h study period. A comparison between these data and the results obtained with tropisetron alone suggested that the combination was more effective than tropisetron in reducing the number of emetic episodes in the whole study period ($P = 0.023$). Latency was not affected by the addition of haloperidol (12 vs. 13 hours in the tropisetron group, $P = 0.305$). Grade of nausea was minor in the tropisetron-haloperidol treated patients, with a better control in comparison to tropisetron group ($P = 0.004$).

Table 4. Events related to antiemetic treatment

	Headache	Extrapyramidal reactions	Hypotension	Sedation	Modifications of antiemetic treatment: Dose reduction	Modifications of antiemetic treatment: Suspension
All treatments	5 (9)	2 (3)	2 (3)	2 (3)	2 (3)	5 (9)
Alizapride	—	2 (12)	—	1 (6)	1 (6)	1 (6)
Tropisetron	1 (7)	—	1 (7)	—	—	2 (15)
Tropisetron plus haloperidol	4 (16)	—	1 (7)	1 (4)	1 (4)	2 (8)

Number of events (percentage for each antiemetic treatment group).

12 patients received scopolamine in a transdermal formulation in combination with tropisetron plus haloperidol. The addition of scopolamine to tropisetron and haloperidol did not improve the results achieved by the two drugs in combination (data not shown).

Side-effects attributable to antiemetic therapy were mild and reversible (Table 4). 2 patients treated with alizapride presented with extrapyramidal reactions, and one patient presented with sedation. In 1 case alizapride was discontinued because of extrapyramidal reaction. In the group of patients treated with tropisetron or tropisetron plus haloperidol 5 patients presented with headache, 2 presented with hypotension and 1 with mild sedation. In 4 cases the headache was not rapidly controlled by paracetamol, and tropisetron was discontinued. Diarrhoea and minor elevation of liver enzymes were uniformly present in all patients, due to high-dose alkylating agent chemotherapy.

DISCUSSION

The recent introduction in the clinical practice of high-dose chemotherapy protocols, with or without autologous bone marrow transplantation, has increased the need for an effective and safe regimen for prevention of nausea and vomiting. Alkylating agents are known to exhibit a steep dose-reponse curve and can be escalated several times before incurring in the haematopoietic toxicity which may or may not require autologous bone marrow transplantation [12]. Both high-dose cyclophosphamide and high-dose melphalan cause severe nausea and vomiting, only partially relieved by established antiemetics. In our past experience we adopted different modalities for vomiting prevention, i.e. continuous intravenous infusion of prochlorperazine or bolus administration of steroids and/or substituted benzamides (high-dose metoclopramide or alizapride). Both treatments yielded poor control of vomiting. Delivery of high-dose alkylating agent would be made much easier by a safe and effective antiemetic treatment.

Until recently the pathophysiology of chemotherapy-induced vomiting was poorly understood. The relative abundance of dopamine D_2 receptors in the area postrema of the central nervous system led to the utilisation of dopamine antagonists (metoclopramide, phenothiazines, butyrophenones) for prevention of vomiting. However, with the exception of high-dose metoclopramide [13], these drugs either alone or in combination are generally ineffective against severe vomiting. Recent laboratory data had shown the importance of serotonin ($5\text{-}HT_3$) in mediating chemotherapy-induced vomiting, and that selective blockage of $5\text{-}HT_3$ receptors can prevent vomiting induced by cisplatin in ferrets [14]. It has also been recognised that metoclopramide at low doses has an antidopamine activity, but at high doses antagonises $5\text{-}HT_3$ receptors [15]. Several clinical trials have now demonstrated the antiemetic efficacy of potent and selective $5\text{-}HT_3$ receptor antagonists in patients undergoing cancer chemotherapy with cisplatin [16, 17] or other chemotherapeutic agents [18, 19]. Our results suggest that tropisetron effectively ameliorated nausea and vomiting induced by high-dose alkylating agent chemotherapy; however, it did not appreciably increase the percentage of complete responders (13%). Since the vomiting process is too complex to expect a single receptor antagonist to prevent it completely, we associated a dopamine receptor antagonist, haloperidol, to the $5\text{-}HT_3$ receptor antagonist. Haloperidol has a weak antiemetic activity at the low dosage we have utilised in this study; however, it increased the activity of tropisetron without additional side-effects. In the 26 chemotherapy cycles with tropisetron plus haloperidol 6 patients reported complete protection. Median number of emetic episodes was very low in comparison to the traditional antiemetic medication alizapride, and even to tropisetron as single agent. The addition of scopolamine to the combination of tropisetron plus haloperidol did not seem to improve the antiemetic efficacy of the medication, given also the small size of the patient population entered in this pilot study. Other studies have suggested a synergism between a $5\text{-}HT_3$ receptor antagonist, ondansetron, and the steroid dexamethazone [20, 21]. Clearly, prospective randomised studies will be necessary to document these effects.

Side-effects of tropisetron were transient and reversible upon discontinuation of the drug, headache being the most prominent. Other side-effects (hypotension, sedation) were mild and did not require drug discontinuation.

In conclusion, tropisetron is an effective drug in the prevention of high-dose alkylating agent chemotherapy induced vomiting. The addition of haloperidol to tropisetron significantly improved its antiemetic efficacy without additional side-effects. Therefore, clinical results presented here show that the introduction of tropisetron in the clinical armamentarium can improve the therapeutic index of high-dose cancer chemotherapy.

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Ifosfamide and Mitomycin in Combination for the Treatment of Patients with Progressive Advanced Non-small Cell Lung Cancer

Howard Gurney, Edson Sydney de Campos, David Dodwell, Arvind Kamthan and Nicholas Thatcher

42 patients with progressive and advanced non-small cell lung cancer received chemotherapy comprising ifosfamide 1.5 g/m², mesna 1.5 g/m² and mitomycin 1.2 mg/m² daily for 5 days. Only those patients with symptoms and progressive disease were selected for treatment. Partial response was achieved in 10/42 patients (23.8%) and stable disease in 25/42 (59.5%). The Karnofsky performance status (KP) improved in 10/42 patients (23.8%) and a subjective respiratory symptom score improved in 12 patients (28.6%). In addition 27 patients (64.3%) had stabilisation of both the KP and respiratory score following chemotherapy. These results indicate that the ifosfamide and mitomycin combination is active in non-small cell lung cancer in this selected group of patients with antitumour and symptom control activity.
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INTRODUCTION

PATIENTS WITH advanced non-small cell lung cancer have a median survival of less than 12 months with or without chemotherapy [1]. Ifosfamide has been found to be one of the more active agents in this tumour with response rates of 10–30% when used as a single agent [2]. Mitomycin induces a similar response rate in these patients [3]. The policy at this institution is to treat with chemotherapy only those patients with advanced non-small cell lung cancer who have progressive and symptomatic disease. It was in a group of such patients that we assessed a combination of ifosfamide and mitomycin for palliative and antitumour effect.

PATIENTS AND METHODS

Patient characteristics are listed in Table 1. To be eligible, patients were required to have progressive (asssessed by monthly tumour evaluation) and symptomatic disease, be aged 70 years or less, have adequate bone marrow function as assessed by a white cell count (WCC) $\geq 3.0 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l, and have a creatinine clearance >50 ml/min. Karnofsky performance status and the Medical Research Council (MRC) respiratory score [4, 5] were assessed prior to each chemotherapy and 1 month after completion of all treatment. The relationship of disease stage to breathlessness assessed by

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