Singapore Med J 1998; Vol 39(9):396-398

Use of Ondansetron in the Control of Emesis in Autologous Peripheral Blood Stem Cell Transplant (APBSCT) for Solid Tumours

S S Leong, C P Teo, M Tao, P T Ang

ABSTRACT

Aim: The use of autologous peripheral blood stem cell transplant (APBSCT) for solid tumours have increased exponentially in the last 5 years. While the use of 5-hydroxytryptamine 3 (5HT3) receptor antagonists has been shown to improve control of emesis in patients receiving conventional dose chemotherapy, similar literature in APBSCT is more limited. We report our experience in the use of ondansetron in APBSCT.

Method: Twenty-three patients with solid tumours receiving high-dose chemotherapy with APBSCT were studied. All were started on intravenous ondansetron at 24 mg/day before commencement of the conditioning regimen and continued till vomiting had ceased for 24 hours. The conditioning regimen used was dependant on the tumour type and the duration ranged from 4 to 6 days. Control of emesis was assessed by the number of vomiting episodes in each 24-hour period, monitored throughout conditioning till discharge from hospital.

Results: Complete or major protection from vomiting was achieved in 83% of patients on day 1. During the entire conditioning period, 52% of patients achieved complete or major response to ondansetron. After the conditioning period (delayed emesis), 44% of patients achieved complete or major response.

Conclusions: The control of emesis for patients undergoing high-dose chemotherapy with APBSCT is fair with ondansetron. Research on more effective combinations to further improve emetic control in this selected group of patients is needed.

Keywords: high-dose chemotherapy, vomiting, 5HT3 receptor antagonist

Department of Medical Oncology
Singapore General Hospital
Outram Road
Singapore 169608

S S Leong, M Med, MRCP
Registrar

C P Teo, M Med, FAMS
Consultant

M Tao, MRCP, FAMS
Consultant

3 Mt Elizabeth #15-08
Mt Elizabeth Medical Centre
Singapore 228510

P T Ang, M Med, FRCP, FAMS
Consultant Oncologist

Correspondence to:
Dr S S Leong

Division of Haematology/Oncology
Department of Medicine
Medical University of South Carolina
171 Ashley Avenue
Charleston
South Carolina 29425-2225

INTRODUCTION

Chemotherapy-induced nausea and vomiting is still one of the most distressing symptoms associated with the treatment of cancer[3]. There has been tremendous progress made in the management of treatment-induced emesis in the last decade, from the use of high-dose metoclopramide[5], to the use of combination therapy with metoclopramide, dexamethasone and diphenhydramine or lorazepam[8,12]. Complete protection from vomiting reported from such combinations was between 56% – 72% for moderately to highly emetogenic chemotherapeutic agents. The development of the 5-hydroxytryptamine 3 (5HT3) receptor antagonists has been one of the major breakthroughs in the treatment of chemotherapy-induced emesis because of their higher efficacy and relative lack of toxicity.

The evaluation of ondansetron, a 5HT3 receptor antagonist, has mainly been in studies involving the use of conventional chemotherapy[4,6,9,13]. The use of such anti-emetic drugs with much higher doses of chemotherapy involved in autologous peripheral blood stem cell transplant (APBSCT) has been less well studied.

We report our experience in the use of ondansetron in the control of emesis during high-dose chemotherapy with APBSCT for solid tumours.

PATIENTS AND METHODS

Twenty-three patients with solid tumours who underwent high-dose chemotherapy with APBSCT from November 1994 to May 1996 were included in the study. All patients were aged 16 and above and had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 – 2. All the patients had previously been treated with chemotherapy and had shown response to treatment. Their control of emesis had been satisfactory on conventional doses of chemotherapy.

Patients' characteristics are depicted in Table I. All patients received high doses of emetogenic chemotherapy as conditioning regimen before APBSCT. The types of tumour managed are listed in Table II. Patients with breast carcinoma received cyclophosphamide (1500 mg/m^2), thiotepa (125 mg/m^2), carboplatin (200 mg/m^2) in 24 hours of continuous infusions daily for 4 days. Patients with lymphoma received BCNU (15 mg/kg) on day 1, etoposide (60 mg/kg) on day 3 and cyclophosphamide (100 mg/kg) on day 5, each over 4 hours. Patients with soft tissue sarcoma and germ cell tumour received ifosfamide (4000 mg/m^2) daily from day 1 – 3, carboplatin (450 mg/m^2) and etoposide (400 mg/m^2) daily from day 4 – 6, each over 4 hours. Patients with multiple myeloma received cyclophosphamide (1500 mg/m^2) and

Table I – Demographic data of patients

Variables	n = 23
Age	
Range	16 – 58
Median	42
Sex	
Female	12
Male	11
Race	
Chinese	20
Malay	2
Indian	1

Table II – Types of tumours treated

Tumour	No. of patients
Breast carcinoma	8
Lymphoma	9
Multiple myeloma	2
Soft tissue sarcoma	3
Germ cell tumour	1

thiotepa (125 mg/m^2) in 24 hours of continuous infusions daily for 4 days.

All patients were started on intravenous ondansetron 30 mins before commencement of the conditioning regimen, at a dose of 24 mg/day, either as 8 hourly 8 mg boluses or as a continuous infusion. In addition, they could also receive combinations of intravenous dexamethasone, p.o. lorazepam intravenous diphenhydramine and p.o. metoclopramide. Ondansetron was given throughout the conditioning period and discontinued after vomiting has ceased for at least 24 hours.

The patients were managed in isolation rooms and maximal supportive care was given. All had intravenous fluids of at least 3 litres a day. Weight was charted daily and number of vomiting episodes recorded for each 24-hour period. Parenteral nutrition was started if there was rapid weight loss of $>$ 10% or if the patient was unable to retain any food or drinks.

Control of emesis was assessed by the number of vomiting episodes in each 24-hour period. This was monitored till the patient was discharged from the hospital. Complete response was achieved when there was no vomiting in a 24-hour period; major response when there was only one episode of vomiting; minor response when there were two to four episodes; and failure when there were more than four episodes of vomiting[15,16].

The emesis control was assessed in three periods: in the first 24 hours, during conditioning (from the start of chemotherapy), and in the delayed phase which begins 24 hours after completion of chemotherapy [7] until the patient was free of emesis for at least 48 hours. For each period of assessment, the worst day's data was used.

Chi-square test was used to assess variables for possible influence on emetic control. A p value of < 0.05 was regarded as significant.

RESULTS

Twenty-three patients were evaluated for emetic control. In the first 24 hours after commencement of chemotherapy, 19 out of 23 (83%) patients had complete or major response. During the entire period of conditioning, 9 (39%) patients achieved complete and 3 (13%) achieved major response. Nine (39%) patients achieved complete response and 1 (4.4%) major response in the delayed phase (Table III). Overall, 6 (26%) patients had no vomiting throughout the entire conditioning period and the delayed phase while 2 (9%) patients achieved major response in the whole period.

Of the 9 patients who achieved complete response in the conditioning period, 6 (66%) remained free of vomiting in the delayed phase. This is in contrast to patients who had some degree of vomiting in the conditioning period, where only 3 out of 14 (21%) patients had no vomiting in the delayed phase. This means that the patients who achieved complete response in the conditioning period had a much higher chance of remaining free of emesis in the delayed phase.

The duration in which vomiting continued to occur ranged from 0 to 22 days from the start of chemotherapy, with a median of 7 days. Nine (36%) patients required parenteral nutrition due to inadequate oral intake or significant weight loss. There were no adverse effects attributable to the use of ondansetron. The duration of use of ondansetron ranged from 7 to 25 days with a median of 9 days.

Although there appeared to be a trend towards better emetic control (complete and major response) in male patients (64% both during conditioning and during the delayed phase) when compared to females (42% during conditioning and 25% for delayed emesis), this was not statistically significant ($p < 0.05$).

When results of the various tumour types were analysed, there was no significant difference in emetic control for the different regimen used for different tumours (Table IV).

DISCUSSION

With the much higher doses of chemotherapy used for conditioning before APBSCT, more emesis is to be expected during treatment. The efficacy of ondansetron in controlling emesis associated with chemotherapeutic agents at conventional doses cannot be extrapolated to include high-dose conditioning regimen.

There has been some recent studies assessing the ability of 5HT3 receptor antagonists to suppress emesis induced by high-dose chemotherapy before APBSCT. In one study where ondansetron at a dose of 24 – 32 mg was used together with conditioning regimen, complete and major emesis control was achieved in 76% of patients on day 1 of treatment, 58% on day 2 and 52% on day 3[1]. In a randomised study using granisetron; 51% of patients maintained complete and major emesis control throughout the period of conditioning and the results were superior

Table III – Response to ondansetron

Response	No. of patients (%)			
	D1	Conditioning	Delayed	Overall
Complete response	18 (78%)	9 (39%)	9 (39%)	6 (26%)
Major response	1 (4.5%)	3 (13%)	1 (4.5%)	2 (9%)
Minor response	3 (13%)	7 (30.5%)	9 (39%)	9 (39%)
Failure	1 (4.5%)	4 (17.5%)	4 (17.5%)	6 (26%)

Table IV – Response of patients with the various tumour types to ondansetron

Tumour	No. of patients			
	Conditioning		Delayed	
	CR + MA	MI + F	CR + MA	MI + F
Breast	4	4	2	6
Lymphoma	3	6	3	6
Others	5	1	5	1

CR : complete response
MA : major response
MI : minor response
F : failure

to the control group receiving standard anti-emetics[10]. In another study comparing the use of ondansetron to conventional chlorpromazine in transplant patients, similar control of emesis was achieved in both groups, but patients given ondansetron had significantly fewer side effects[2].

In this study, 52% of patients maintained complete or major response to ondansetron during the period of conditioning. The same degree of control of delayed emesis was achieved in 44% of patients. This was comparable to results of similar studies done earlier. When there was complete control of emesis in the early period (during the conditioning period), the chance of remaining free of vomiting in the delayed phase was significantly better.

Seynaeve et al[14] and other investigators[11,12] have shown that females, irrespective of chemotherapy type, have a lower response rate to anti-emetic agents. A similar trend was observed in this study but did not reached statistical significance. This is perhaps due to the small sample size.

Overall, 65% of patients had at least 2 episodes of vomiting in at least one day during the conditioning regimen and in the period after chemotherapy. Even though the use of 5HT3 receptor antagonists like ondansetron had shown benefits when compared to conventional anti-emetics in terms of response as well as toxicity profile in previous studies, there is more to be desired for symptom control in this special group of patients. A continued search for more effective anti-emetic combinations or newer agents will hopefully result in further improvement in morbidity associated with APBSCT as well as a better quality of life for our patients.

REFERENCES

1. Barbounis V, Koumakis G, Vassilomanolaki M, et al. A phase II study of ondansetron as antiemetic prophylaxis in patients receiving high-dose polychemotherapy and stem cell transplantation. Support Care Cancer 1995; 3(5):301-6.
2. Bosi A, Guidi S, Messori A, et al. Ondansetron versus chlorpromazine for preventing emesis in bone marrow transplant recipients: a double-blind randomized study. J Chemother 1993; 5(3):191-6.
3. Coates A, Abraham S, Kaye SB, et al. On the receiving end - patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol 1983; 19:203-8.
4. De Mulder PHM, Seynaeve C, Vermorken JAB, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicenter, randomized, double-blind, cross over study. Ann Intern Med 1990; 113:8334-40.
5. Gralla RJ, Itri LM, Pisko SE, et al. Anti-emetic efficacy of high dose metoclopramide: randomized trials with placebo and prochloperazine in patients with chemotherapy-induced nausea and vomiting. N Engl J Med 1981; 305:905-9.
6. Hainsworth J, Harvey W, Pendergrass K, et al. A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. J Clin Oncol 1991; 9:721-8.
7. Hesketh PJ, Gandara DR. Serotonin antagonists: a new class of antiemetic agents. J Natl Cancer Inst 1991; 83:613-20.
8. Kris MG, Gralla RJ, Clark RA, et al. Antiemetic control and prevention of side effects of anticancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone. A double-blind randomized trial. Cancer 1987; 60:2816-22.
9. Marty M, Pouillart P, Scholl S, et al. Comparison of the 5-hydroxytryptamine 3 (serotonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. N Engl J Med 1990; 322:816-21.
10. Okamoto S, Takahashi S, Tanosaki R, et al. Granisetron in the prevention of vomiting induced by conditioning for stem cell transplantation: a prospective randomized study. Bone Marrow Transplant 1996; 17:679-83.
11. Roila F, Boschetti E, Tonato M, et al. Predictive factors of delayed emesis in cisplatin-treated patients and antiemetic activity and tolerability of metoclopramide or dexamethasone: a randomized single-blind study. Am J Clin Oncol Cancer Clin Trials 1991; 14(3):238-42.
12. Roila F, Tonato M, Basurto C, et al. Protection from nausea and vomiting in cisplatin-treated patients: high-dose metoclopramide combined with methylprednisolone versus metoclopramide combined with dexamethasone and diphenhydramine: a study of the Italain Oncology Group for Clinical Research. J Clin Oncol 1989; 7:1693-700.
13. Seynaeve C, De Mulder PH, Lane Allman E, et al. The 5-HT3 receptor antagonist ondansetron re-establishes control in refractory emesis induced by non-cisplatin chemotherapy. Clin Oncol R Coll Radiol 1991; 3(4):199-203.
14. Seynaeve C, Schuller J, Buser K, et al on behalf of the Ondansetron Study Group. Comparison of the anti-emetic efficacy of different doses of ondansetron, given as either a continuous infusion or a single intravenous dose, in acute cisplatin-induced emesis. A multicenter, double-blind randomized parallel group study. Br J Cancer 1992; 66:192-7.
15. Smith IE on the behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving moderately emetogenic cytotoxic chemotherapy. Eur J Cancer 1990; 26:19S-23S.
16. Soukop M on the behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving high-dose cisplatin. Eur J Cancer 1990; 15S-19S.