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Original Research Article

Palonosetron for the prevention of chemotherapy induced nausea and vomiting: a comparative study in a tertiary care hospital from India

Shubhatara Swamy[1]*, Vijaya Rajendran[1], Durga Prasan[2], Pratibha Nadig[1]

[1]Department of Pharmacology, [2]Department of Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India

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***Correspondence to:**
Dr. Shubhatara Swamy,
Email: shubhadpak@gmail.com

ABSTRACT

Background: Despite advances in symptom management, chemotherapy-induced nausea and vomiting (CINV) remains one of the most dreadful consequences of cancer therapy.
Methods: The study was carried out at Medical Oncology Department, Vydehi Institute of Medical Sciences and Research Centre, Bangalore. Hundred and forty-four cancer patients of either sex, aged 18-65 years with adequate blood counts requiring moderately emetogenic chemotherapy (MEC) as per Hesketh classification were included. The patients were prospectively divided into two groups before the initial cycle of chemotherapy. Patients in Group A (n=71) received ondansetron, and dexamethasone along with aprepitant capsules, Whereas, Group B (n=73) received palonosetron, and dexamethasone along with placebo capsules, 30 min before chemotherapy. Thereafter the patients were administered with the drugs and observed for nausea and vomiting. The efficiency of both regimens was assessed by adopting validated functional living index emesis (FLIE) questionnaire. Analysis of the data was done using the SPSS 21.0 software.
Results: The mean age of the patients was 40.5 years and the male to female ratio was 1:2.4. In all the patients, no changes were detected in the ECG readings after MEC. The nausea and vomiting score were comparable in both groups. No significant difference ($p>0.05$) was noticed between group A and group B in both mm and in FLIE points. No serious adverse events were found relating to antiemetic treatment.
Conclusions: Palonosetron in combination with corticosteroids was non inferior to ondansetron in combination with aprepitant and corticosteroids in controlling acute and delayed stages of CINV in patients requiring MEC. Thus, it can be recommended as first-line therapy for patients treated with MEC.

Keywords: Chemotherapy induced nausea and vomiting, Functional life index-emesis, Palonosetron, Aprepitant

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common treatment related undesirable side effect of cancer treatment.[1,2] Around 70-80% of the patients receiving chemotherapy experience CINV with a substantial negative impact on patient quality of life, can possibly lead to decreased tolerability to subsequent chemotherapy cycles, early discontinuation of anticancer therapy, treatment failure or increased medical complications.[3-7] CINV can occur within 24 hours of chemotherapy (acute) or after 24 hours of chemotherapy (delayed) or before the start of chemotherapy (anticipatory). The severity of illness varies substantially depending on the emetogenic potentiality of the chemotherapeutic agents, enduring risk factors, and the efficacy of antiemetic regimen.[8,9]

The emetogenicity of chemotherapeutic agent differs considerably based on the specific antineoplastic agent used, route of administration, dose and treatment plan. The chemotherapeutic regimens are broadly categorized into four types, rendering to risk probability of inducing emesis: high emesis (>90%) for cisplatin, mechlorethamine, dacarbazine, cyclophosphamide, and streptozotocin and others; moderate emesis (30~90%) for cyclophosphamide, oxaliplatin, cytarabine, irinotecan and doxorubicin agents, etc., low emesis (10~30%) for

mitomycin C, methotrexate, paclitaxel, trastuzumab, cetuximab, etc., and minimal emesis (<10%) for vinblastine, bleomycin, and others.[10]

Several anti-emetic drugs, for example, dopamine antagonists, benzodiazepines, corticosteroids, neuroleptics and cannabinoids 5-hydroxytryptamine receptor (subtype 3) antagonists ($5HT_3$RAs), neurokinin-1 receptor antagonists (NK-1RA), have been used for the prevention and treatment of CINV.[11] Regardless of extensive advances in antiemetic treatment over the previous two decades, CINV prevention continued as a challenge in clinical practice.[12-14]

According to standard antiemetic guidelines, use of $5HT_3$RAs such as ondansetron, granisetron and dolasetron in combination with NK-1RAs and dexamethasone is recommended for patients receiving highly emetogenic chemotherapy (HEC).[15] Whereas, $5HT_3$RAs in combination with dexamethasone is recommended for patients receiving moderately emetogenic chemotherapy (MEC).[15] However, due to the assertive treatment for cancer patients and failure of implementation of the antiemetic guidelines, chemotherapy induced side effect (emesis) has prompted misuse of NK-1RA (Aprepitant) for patients receiving MEC which is not financial for patients. In several studies, Aprepitant indicated improved antiemetic action in combination with $5HT_3$RAs and dexamethasone, thus it gained importance in antiemetic prophylaxis.[16,17]

In 2007, palonosetron ($5HT_3$RA) a new drug was approved by drug controller general of India for the prophylaxis of nausea and vomiting associated with initial and repeat courses of moderately and HEC.[18] This potent drug has receptor binding affinity of above 30-fold and plasma half-life exceeding 40 hrs. Even though this drug is effectual, it is not popularly utilized by the health care professional.[19]

In India, the literature on antiemetic prophylaxis in patients receiving HEC is well standardized and clear; however, studies evaluating the role of newer antiemetics in the prevention of CINV in patients receiving MEC is particularly limited. The ideal antiemetic prophylaxis in MEC is also less clear and moreover the role of aprepitant and palonosetron are not clearly determined in MEC so far. Hence, in our study, we compared the antiemetic efficacy of two different regimens namely $5HT_3$RA (palonosetron) and with Corticosteroid against Ondansetron and NK-1RA (aprepitant) in patients requiring MEC in controlling CINV.

METHODS

Study design

This prospective non-randomized open-label study was carried during October 2009 to June 2011 over a period of one and a half years in the Medical Oncology Department at a Medical College and Research Centre in Bangalore after receiving permission from the institutional ethics committee.

Study population

Patients attending out-patient clinic of Medical Oncology Department, who underwent assessment of cancer with diagnosis of type and staging.

Selection criteria

Patients of either sex, aged 18-65 years with adequate blood counts requiring MEC as per Hesketh classification, who were willing to participate in the research study were included whereas, patients with cardiac impairment, hypokalaemia, hypomagnesaemia, multifactorial nausea and vomiting requiring HEC and LEC, patients on diuretics, anti-arrhythmic drugs and high dose anthracyclin therapy, patients who received chemotherapy/radiotherapy in the past 10 days, patients, who are alcoholics and also those who consumed alcohol 24hrs preceding to chemotherapy were not considered for the study.[20] Informed consent was obtained from all the patients, who fulfilled the inclusion criteria.

Study procedure

All the patients (n=144) were divided in to two groups, Group A and B.

Group A (n=71) received ondansetron (8 mg on day1 intravenously (i.v)), and dexamethasone (8mg day1, followed by 4 mg twice daily (BD), orally on day 2, 3, 4) along with aprepitant capsules (oral, 125 mg on day 1, 80 mg on day 2, and 80 mg on day 3).

Group B (n=73) received palonosetron (0.5 mg slow i.v bolus, day 1), dexamethasone (i.v, 8 mg day 1, followed by 4 mg BD, orally day 2, 3, 4) and placebo capsules (oral, day 1, day 2, day 3).

Thirty minutes thereafter the patients were administered with the chemotherapy drugs and observed for nausea and vomiting.

All the drugs used in this study were known to prolong QT interval, hence electrocardiogram was done before and after chemotherapy. Further, before the start of chemotherapy, the blood parameters total haemoglobin (Hb), white blood cell (WBC) count, neutrophil count and platelet count were assessed in all the patients. Patients with Hb of 9 gm/dl and above, WBC count not less than 4000 cells/cumm, neutrophil count 1500 cells/cumm and platelets not less than 100000 cells/cumm were only allowed for chemotherapy.

Efficacy of the study regimens were evaluated by using validated functional living index emesis (FLIE) scale.[21] All the patients were given with FLIE questionnaire

booklet to record their observations from day 0 to day 5 of chemotherapy about nausea and vomiting. After collection of the booklets, they were questioned again about their nausea and vomiting experiences and adverse reactions if any. The same was recorded separately. Use of rescue medications for breakthrough and refractory emesis was also recorded.

The FLIE scale used in this study comprised of two fields (vomiting and nausea) with nine indistinguishable items in each i.e., nausea (questions 1-9) and vomiting (questions 10-18). Each question is to be marked on a 100 cm visual analogue scale (VAS) graded from 1 to 7.

For each question, the VAS score was measured by putting a metric ruler below the line for the question so that the "0" on the ruler is directly below the left-hand end of the line. The distance to where the patient has marked his or her vertical mark (l) through the line is measured. The minimal score for any question is '0' and the maximal score is '100'.

RESULTS

Data analysis has been carried out using SPSS 21.0 software. Independent t test has been performed to find difference between two groups in the FLIE score and p value less than 0.05 was considered statistically significant.

Hundred and forty-four patients were involved in the study and the distribution of the patients was almost equal in both groups i.e., 71 patients in Group A and 73 patients in Group B. The mean age of the patients was 40.5 years with SD of ±18.13 and the male to female ratio was 1:2.4 (29.2% vs. 70.8%) (Table 1).

Table 1: Distribution of patients based on age and gender.

	Group A	Group B	Total
	N (%)	N (%)	N (%)
Age in years			
18-20	2 (2.8)	4 (5.5)	6 (4.2)
21-30	22 (30.9)	20 (27.4)	42 (29.2)
31-40	9 (12.7)	10 (13.7)	19 (13.2)
41-50	22 (30.9)	21 (28.8)	43 (29.9)
51-60	16 (22.5)	17 (23.3)	33 (22.9)
61-70	0 (0.0)	1 (1.4)	1 (0.7)
Gender			
Male	17 (23.9)	25 (34.2)	42 (29.2)
Female	54 (76.1)	48 (65.8)	102 (70.8)

N=no. of patients.

The blood parameters were within the required guidelines of MEC (Table 2). Further in all the patients (both groups), no changes were detected in the ECG readings after MEC.

Table 2: Average blood parameters before MEC.

Blood parameters	Group A (Mean)	Group B (Mean)
Hemoglobin percentage (mg/dl)	10.07	10.13
WBC count (cell/cu mm)	5590.14	5443.83
Neutrophils count (cell/cu mm)	1837.32	1743.42
Platelet count (cell/cu mm)	135905.06	139048.6

The nausea score was comparable in both groups. No significant difference ($p>0.05$) was noticed between group A (aprepitant and ondansetron) and group B (palonosetron) in both mm and in FLIE points (Table 3).

Table 3: Mean nausea score in mm and FLIE points.

Nausea score	Group A (n=71)	Group B (n=73)	P value
In mm	816.61±176.74	836.86±170.43	0.485
In FLIE points	57.99±10.60	58.23±10.16	0.478

The vomiting score was similar in both groups. No significant difference ($p>0.05$) was noticed between group A (aprepitant and ondansetron) and group B (palonosetron) in both mm and in FLIE points (Table 4).

Table 4: Mean vomiting score in mm and FLIE points.

Vomiting score	Group A (n=71)	Group B (n=73)	P value
In mm	824.04±184.48	828.63±187.09	0.882
In FLIE points	58.72±10.64	58.82±11.05	0.953

One patient in group A experienced hiccups and two patients in group B had mild rashes; however, the symptoms were mild and no treatment was required, as patient did not report to the hospital. Further, none of the patient experienced refractory or breakthrough nausea and vomiting, so there was no requirement for rescue medications. No serious adverse events were found relating to antiemetic treatment.

DISCUSSION

CINV is one of the most prevalent side effects of chemotherapy. At present, aprepitant (NK-1RAs) in combination with dexamethasone and $5HT_3$ antagonist has been demonstrated to be more efficient than other 5-HT_3 antagonists in patients receiving both HEC and MEC.[16,17] However, it is less recommended, since it is very expensive thus, it has become financial burden for the patients receiving chemotherapy. Palonosetron is found to be effective in controlling acute and delayed CINV in patients requiring HEC, with less toxic profile.[22] However, none of studies compared $5HT_3$RA

(palonosetron) and NK-1RA (aprepitant) in patients requiring MEC. Hence, this investigation has been conducted.

In this study, the combination of palonosetron and dexamethasone was found to be non-inferior to ondansetron in combination with aprepitant and dexamethasone in the management of CINV in patients requiring MEC. This is in harmony with the literature that have reported in combination treatment using a $5HT_3$ receptor antagonist, an NK-1 receptor inhibitor, and dexamethasone is useful for prevention of the CINV caused by HEC.[23,24] In this study palonosetron exhibits an extended activity that may be related to its long half-life and its sole interaction with the $5HT_3$ receptor.

The findings from prior studies on first-generation $5HT_3$RAs suggest that cancer patients who are administered with antineoplastic drugs might be at high risk of experiencing cardiac adverse events including arrhythmia, since antineoplastic drugs can induce ECG alterations such as prolongation of the QT interval or pulse rate and decrease of heart rate.[21] According to published report, one reason for adverse cardiac events seems to be a due to ECG changes-QT prolongation or PR prolongation.[26] Prospective studies demonstrated, minor reversible, clinically non-significant ECG changes for the study drugs ondansetron, aprepitant and palonosetron.[27,28] However, in our study no changes were observed in ECG parameters for the study drug palonosetron. These findings are partially in agreement with Musso et al, who found no fluctuations in ECG parameters after palonosetron infusion. Thus, palonosetron seems to have no serious arrhythmogenic effect related to cardiac repolarization.[29]

As per the published studies, constipation and headache are the most commonly reported adverse events for first and second generations 5-HT_3 RAs. However, in this study hiccups (1.3%) and rashes (2.7%) are the adverse events that are reported in palonosetron and aprepitant groups, respectively, but they are mild and non-serious and no treatment was needed.[30,31] Further, no serious adverse events were reported by study patients. These results are comparable with Musso et al, who compared palonosetron (Aloxi® at a dose of 0.25 mg) and dexamethasone for the prevention of acute and delayed emesis in patients receiving multiple-day chemotherapy.[29] Thus, the study reveals that palonosetron in combination with dexamethasone was found to be very promising therapy for control of CINV in patients receiving MEC because palonosetron is more cost effective and the drug is administered as single dose through iv route.

CONCLUSION

Palonosetron in combination with corticosteroids was non inferior to ondansetron in combination with aprepitant and corticosteroids in controlling both acute and delayed phases of CINV in patients requiring MEC. Thus, it can be recommended as first-line therapy for patients treated with MEC. Hence, we conclude that palonosetron is the better antiemetic regimen than ondansetron and Aprepitant in controlling acute and delayed phases of CINV.

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