



RESEARCH ARTICLE

EFFECT OF ORAL PALONOSETRON IN IMPROVING QUALITY OF LIFE AS COMPARED TO OTHER ORAL 5HT-3 ANTAGONISTS IN DELAYED CINV IN PATIENTS OF BREAST CANCER

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ABSTRACT

Introduction: The primary objective was to prevent delayed chemo induced nausea and vomiting (CINV). The primary efficacy end point was complete Response (CR) and improving quality of life (QOL).

Material and Methods: This is a prospective, observational study conducted on 45 previously untreated histopathologically-proven patients of ductal carcinoma of Breast from January to December 2015. In this study the patients were selected based on our inclusion criteria and each cohort was composed of 15 breast carcinoma diagnosed patients, each cohort receiving Oral Ondansetron 4 mg TDS(cohort 1) ; Oral Granisetron 1 mg BD(cohort 2) ;Oral Palonosetron 0.5 mg OD(cohort 3)and after standard protocol based chemotherapy from day 3 to day 7 post chemotherapy for the prevention of Delayed CINV. and were asked to keep a vomiting diary ,interviewed on telephone and on next follow up visit and then results were graded according to the response obtained by each individual. Patients with history of allergy to 5HT-3antagonists, any associated medical condition causing nausea/vomiting were excluded.

Results: A total 165 patients were included in the study, In Palonosetron Cohort 98% patients of H&N have CR and 33% in Cx in Cisplatin based chemotherapy and 64%in Anthracyclin based chemotherapy in Breast Cancer patients. Granisetron Cohort; H& N 53%, Cx 22%. Breast 84%. Ondansetron Cohort; H&N 29%, Cx 13 % Breast 57%.

Conclusion: This study shows that oral Palonosetron is better than other oral 5HT-3 antagonists to prevent delayed CINV and thereby improving QOL in patients on chemotherapy.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most distressing side effects of chemotherapy in breast cancer patients which can result in poor compliance to therapy that may in turn affect overall survival. Multi agent regimens are considered standard practice over single agent regimens, and the EBCTCG overview has confirmed the improved recurrence and survival outcome observed with Anthracycline based regimens for management of breast carcinoma (John E. Niederhuber, 2013) which is moderately emetogenic. Since their introduction into routine clinical practice, 5-HT3 receptor antagonists (RAs) have become the cornerstone of current antiemetic prophylaxis and are an integral part of preventive strategies for chemotherapy induced nausea and vomiting (CINV). The currently approved 5-HT3RAs include ondansetron, granisetron, tropisetron, dolasetron, palonosetron, ramosetron, and azasetron.

Poor control of acute CINV is an established predictor for delayed CINV that typically peaks in severity between day 2 and day 4, post chemotherapy, depending on the emetogenic profile of the agent(s) used (Aapro *et al.*, 2006). Although the severity is decreased in delayed CINV in comparison with acute nausea and vomiting, the course can be more protracted, resulting in significant difficulties with hydration, nutrition, and performance status thus impairing quality of life (John E. Niederhuber, 2013). This study was undertaken with the primary objective of preventing delayed chemotherapy induced nausea and vomiting (CINV) with the aim of achieving complete Response (CR) and improving quality of life (QOL).

MATERIAL AND METHODS

The study design was that of prospective, observational study conducted on previously untreated 45 patients of histopathologically proven ductal carcinoma of Breast, who had attended Department of Radiotherapy, Gandhi Medical College and Hamidiya Hospital, Bhopal from January to

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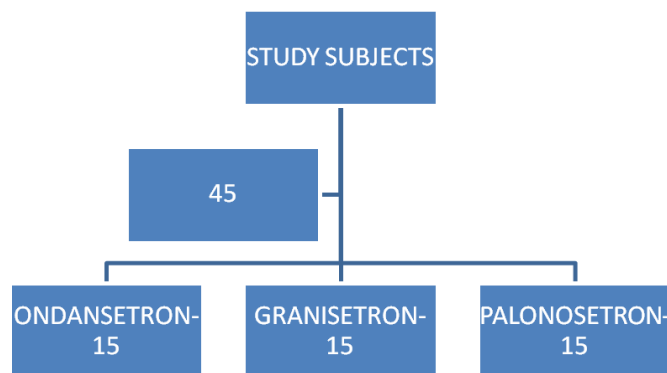
December 2015. Inclusion criteria for the study: 1) patients with age less than 70 yrs ,both sexes2)histologically proven cases of ductal carcinoma,3)karnofsky performance score/scale less than or equal to 70.4)normal haematological,renal,liver function tests and normal chest x ray.

Excusion criteria for the study was : 1)age more than 70 yrs,2)prior irradiation or surgery,3)histology other than ductal carcinoma

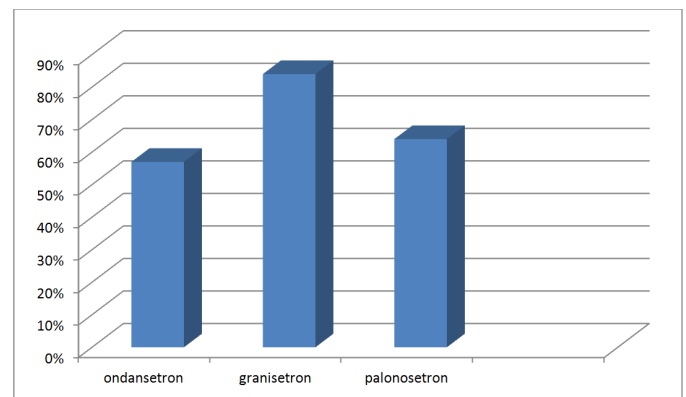
Standard protocol based Anthracycline based chemotherapy for breast cancer which is moderately emetogenic was administered to all of the patients. Cyclophosphamide, Adriamycin and 5 Fluorouracil was one of the multiagent regimen used and other was Paclitaxel, Adriamycin and Cylophosphamide. These patients were divided into three cohorts and each cohort was composed of 15 diagnosed cases of ductal carcinoma patients. all patients were prescribed oral 5HT₃ antagonists, Oral Ondansetron 4 mg TDS was given in cohort 1; Oral Granisetron 1 mg BD given to cohort 2 patients; and Oral Palonosetron 0.5 mg OD given to the cohort 3 from day 3 to day 7 post chemotherapy for prevention of delayed CINV. For evaluation patients were asked to keep a vomiting diary, interviewed on telephone and on next follow up visit for episodes of vomiting and how did it affect their daily routine work. Then results were graded according to the response obtained by each individual. Patients with history of allergy to 5HT-3antagonists, any associated medical condition causing nausea/vomiting were excluded.

RESULTS

A total of 45 patients of ductal carcinoma breast, receiving chemotherapy were enrolled. Of these, 15 patients received oral Ondansetron 4mg TDS (cohort-1). 15 patients received oral Granisetron 1mg BD (cohort-2) and 15 patients received oral Palonosetron 0.5mg OD (cohort-3) from day 3 to day 7 for prevention of delayed CINV.



The results were analysed on the basis of response obtained from the study subjects. They were graded as complete response when they did not have complaint of nausea and vomiting. Complete response rate was 84% among the patients who received Granisetron ie. cohort 2, 64% complete response rate among the patients who received Palonosetron ie. cohort 3, as compared to complete response rate was 57% among the patients who received ondansetron ie. Cohort 1. Thus, as compared to other 5HT₃ receptor antagonists, granisetron has better response in prevention of chemotherapy induced nausea and vomiting in patients of ductal carcinoma breast receiving Anthracyclin based chemotherapy.



- 57% patients in ondansetron cohort had complete response.
- 84% patients in granisetron cohort had complete response.
- 64% patients in palonosetron cohort had complete response.

DISCUSSION

Vomiting results from stimulation of a multistep reflex pathway controlled by the brain, and is triggered by afferent impulses to the vomiting center (located in the medulla) from the chemoreceptor trigger zone; pharynx and gastrointestinal tract (by way of vagal afferent fibers); and cerebral cortex. The chemoreceptor trigger zone, vomiting center, and gastrointestinal tract have many neurotransmitter receptors. Activation of these receptors by chemotherapeutic agents or their metabolites may be responsible for chemotherapy-induced emesis. Principal neuroreceptors involved in the emetic response are serotonin (5-hydroxytryptamine (5-HT₃)) and dopamine receptors other neuroreceptors include acetylcholine, corticosteroid, histamine, cannabinoid, opiate, and neurokinin-1 (NK-1) receptors, which are located in the vomiting and vestibular centers of the brain (David *et al.*, 2009). Nausea and/or vomiting induced by chemotherapy is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory. Delayed-onset nausea and/or vomiting develops in patients more than 24 hours after chemotherapy is administered and commonly occurs when cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin are used. In general, to provide maximal protection against chemotherapy-induced emesis, antiemetic therapy should be initiated before chemotherapy and continued for the duration of the emetic activity according to the chemotherapeutic agent being used (David *et al.*, 2009).

To date, Aprepitant and Palonosetron have been reported to exhibit effective delayed antiemetic effects. However, the efficacy of these agents in combination has not been investigated. For acute-phase emesis, the two receptors are associated with vomiting. However, in the case of delayed emesis, the impact of substance P is considered to become dominant, which is regarded to be a cause for limited antiemetic action of 5-HT₃ receptor antagonists for delayed vomiting. Palonosetron and Granisetron are 5-HT₃ receptor antagonist antiemetic agents. PALO differs from conventional drugs as it has an extremely long half-life in the blood (~40 h), as well as high affinity and selectivity for 5-HT₃ receptors. Thus, it has been identified to be efficacious for the treatment of delayed nausea and vomiting, which occur ≥ 24 h following chemotherapy (Hideyuki Ohzawa *et al.*, 2015).

The current study provides evidence that Palonosetron given to patients receiving highly emetogenic chemotherapy has clinical and statistical superiority in preventing chemotherapy induced nausea and vomiting as compared to ondansetron but less effective as granisetron. In the study, Palonosetron was given in a dose of 0.5mg single dose which was found to be more effective as compared to ondansetron 4mg thrice a day. 64% patients in palonosetron cohort had complete response as compared to 84% patients in granisetron (1mg twice a day) cohort who had complete response. Ohzawa et al. (2015) also reported that there were no significant differences in the incidence of CINV in breast cancer patients who received palonosetron and granisetron (Satoe Fujiwara *et al.*, 2015). This was against the study done by Chan et al. (2011) and Saito et al. (2009) where they proved palonosetron to be superior than granisetron in preventing chemotherapy induced nausea and vomiting. The limitation of this study was the limited number of study subjects. More number of subjects are needed to have a better comparison among the 5HT3 receptor antagonists in preventing chemotherapy induced nausea and vomiting.

Conclusion

Breast cancer constitutes a significant proportion of the patient population in which chemotherapy is commonly indicated. The adjuvant chemotherapies for breast cancer usually involve moderately to highly emetogenic agents and regimens. Since most of the chemotherapy regimens for breast cancer are of moderate emetogenic potential, optimization of an antiemetic regimen would significantly improve quality of life and potentially increase patients' acceptability and tolerability of chemotherapy, thereby allowing an increase in the completion rate of planned treatment which has been shown to improve survival (Vicky, 2011). In this study, oral granisetron at a dose of 1mg BD was found to have better response as compared to other 5 HT-3 receptor antagonists. The evaluation of vomiting and nausea is difficult; however, the evaluation of complete response was possible via the use of patient logs and survey questionnaires.

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