

Impact of oral palonosetron in improving quality of life as compared to other oral 5-HT₃ antagonists in delayed chemotherapy induced nausea and vomiting in patients of head and neck cancer

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ABSTRACT

Background: Chemotherapy induced nausea and vomiting (CINV) remains one of the most common and debilitating complications of highly emetogenic chemotherapy (HEC). This study was undertaken to evaluate palonosetron against other 5-HT₃ receptor antagonists in preventing delayed CINV with the aim of achieving complete response (CR) and improving quality of life (QoL).

Methods: This was a prospective, observational study conducted on 75 histopathologically proven patients of squamous cell carcinoma of Head and Neck (H&N), who came to the Department of Radiation Oncology, Gandhi Medical College and Hamidia Hospital, Bhopal from January to December 2015. Standard protocol based chemotherapy containing highly emetogenic cisplatin based chemotherapy was administered to all the patients. For prevention of delayed chemotherapy induced nausea and vomiting all patients were prescribed oral 5-HT₃ antagonists. Oral Ondansetron 4mg TDS was given to cohort 1, oral Granisetron 1 mg BD to cohort2 and oral Palonosetron 0.5mg OD was given to cohort 3. They were graded as complete response when they did not have complains of nausea and vomiting.

Results: In Ondansetron, Granisetron and in Palonosetron cohort 29%, 53% and 98% patients had complete response.

Conclusions: Palonosetron appears superior. Our study was conducted on handfull of patients and compared palonosetron against only two 5-HT₃ receptor antagonists, so a larger study is suggested to establish the efficacy and better response of palonosetron.

Keywords: Delayed CINV, Complete response, Head and neck cancer, Quality of life

INTRODUCTION

Despite significant progress in its management, chemotherapy-induced nausea and vomiting (CINV) remains one of the most common and debilitating complications of highly emetogenic chemotherapy

(HEC).¹ Nausea and vomiting has been classified as acute, delayed, anticipatory, breakthrough, refractory, and chronic. Acute nausea and vomiting is the nausea & vomiting experienced during the first 24 hours after chemotherapy administration. Delayed CINV occurs after the acute phase that peaks in 2–3 days and can last upto 1 week.² Chemotherapy damages the gastrointestinal

mucosa, causing the release of serotonin (5-hydroxytryptamine 5-HT) from enterochromaffin cells in the small intestine, which, in turn, activates 5-HT₃ receptors located on vagal afferents. Activated vagal afferent fibres send signals to the brain stem vomiting centres, initiating emesis.³ As 5-HT₃ receptors play a key role in pathophysiology of CINV, 5-HT₃ receptor antagonists have been used for prevention of the same. Various pharmacological agents used are ondansetron, granisetron, dolasetron and palonosetron. Palonosetron is highly selective and has high affinity for 5-hydroxytryptamine (5-HT₃) receptors. It has a substantially longer plasma half-life (~40 h) than the other 5-HT₃ receptor antagonists (~10 h). It is proposed that palonosetron exhibits allosteric binding and positive cooperativity, and that this in turn triggers a receptor internalization of 5-HT₃ receptors resulting in a long-lived inhibition of receptor function.⁴

Thus, this study was undertaken to evaluate palonosetron against other 5-HT₃ receptor antagonists in preventing delayed chemotherapy induced nausea and vomiting (CINV) with the aim of achieving complete response (CR) and improving quality of life (QOL).

METHODS

This was a prospective, observational study which was conducted on 75 histopathologically proven patients of squamous cell carcinoma of Head and Neck (H&N), who came to the Department of Radiation Oncology, Gandhi Medical College and Hamidia Hospital, Bhopal, during a 12 months period from January to December 2015. Patients were previously untreated.

For this study the patients were selected based on the inclusion criteria.

Inclusion criteria

- Patients with age less than 70 years
- Both sexes
- Histologically proven cases of squamous cell carcinoma
- Karnofsky performance score/scale more than or equal to 70
- Normal haematological, renal
- Liver function tests
- Normal chest x-ray

Patients with history of allergy to 5HT-3 antagonists, any associated medical condition causing nausea/vomiting, age more than 70 years, history of prior irradiation or surgery and histology other than squamous cell carcinoma were excluded.

These patients were divided into three cohorts each cohort comprising 25 patients.

Standard protocol based chemotherapy containing highly emetogenic cisplatin based chemotherapy was administered to all the patients. For prevention of delayed chemotherapy induced nausea and vomiting all patients were prescribed oral 5-HT₃ antagonists. Oral Ondansetron 4 mg TDS was given to cohort 1; Oral Granisetron 1 mg BD given to cohort 2; and oral Palonosetron 0.5 mg OD to the cohort 3 from day 3 to day 7. The patients were asked to keep a vomiting diary, were interviewed on telephone and on next follow up visit and then results were graded according to the response obtained by each individual.

Evaluation criteria

The CR (complete response) to delayed vomiting was defined as no occurrence of vomiting at all times post chemotherapy without usage of salvage medications.⁵

Statistical analysis was done with SPSS v20 and data was analysed in Microsoft excel sheet.

RESULTS

A total of 75 patients of squamous cell carcinoma of head and neck (H&N), receiving highly emetogenic chemotherapy were enrolled. Of these, 47 were males and 28 were females (M:F= 1.67:1). The mean age of patients was 47 years. Of all the cases, 25 patients received oral Ondansetron 4 mg TDS (cohort-1), 25 patients received oral Granisetron 1 mg BD (cohort-2) and 25 patients received oral Palonosetron 0.5 mg OD (cohort-3) from day 3 to day 7 for prevention of delayed CINV.

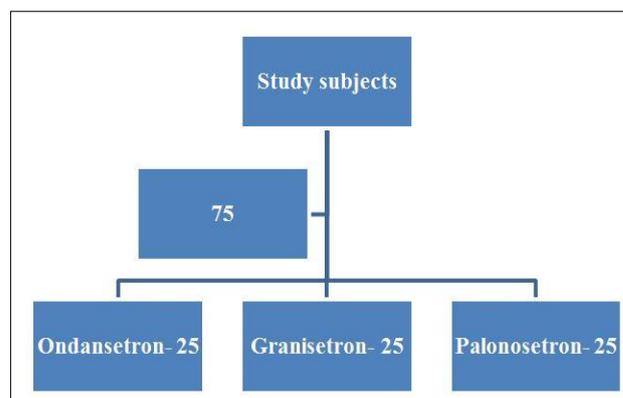


Figure 1: Flow chart showing distribution of patients in each arm.

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.

In Ondansetron cohort on an average 29% patients, in Granisetron cohort on an average 53% patients and in Palonosetron cohort on an average 98% patient had complete response (Figure 2).

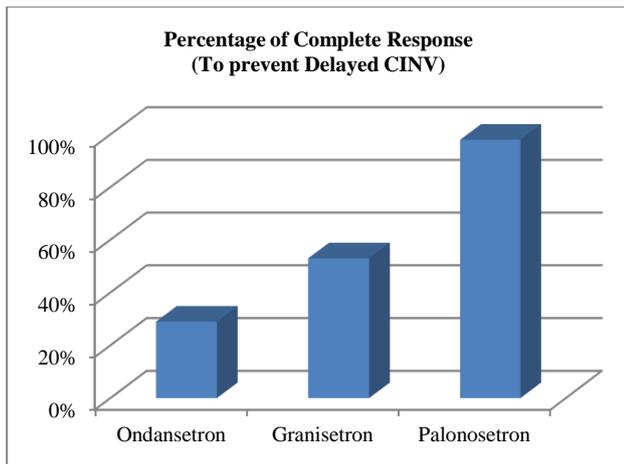


Figure 2: Percentage of patients showing CR with oral 5-HT₃ antagonists.

Thus, as compared to other 5-HT₃ receptor antagonists, Palonosetron had better response in prevention of delayed chemotherapy induced nausea and vomiting.

DISCUSSION

Vomiting is triggered when afferent impulses from the cerebral cortex, chemoreceptor trigger zone (CTZ), pharynx, and vagal afferent fibers of the gastrointestinal tract travel to the vomiting center, which is located in the medulla. Efferent impulses then travel from the vomiting center to the abdominal muscles, salivation center, cranial nerves, and respiratory center, thereby causing vomiting.⁶ The main neurotransmitter receptors involved in this signalling are serotonin (specifically 5-HT₃), neurokinin-1 (NK-1), and dopamine receptors. During chemotherapy, serotonin is released and activates the 5-HT₃ receptors which are present predominantly on the peripheral terminals of vagal afferents in the gastrointestinal tract and in CTZ that lies in the area postrema outside of the blood-brain barrier. The CTZ signals to another area, the nucleus tractus solitarius, in the brain stem that also receives emetogenic stimuli from higher brain centers (e.g., cortical and vestibular) as well as gastrointestinal tract.²

Agents with the highest emetogenic potential which result in emesis during the first 24 hours post-chemotherapy (acute CINV) include cisplatin, high dose cyclophosphamide, carmustine, dacarbazine and mechlorethamine.^{5,6} Risk factors for CINV include the emetogenic potential of the specific drug, the dose used, the treatment schedule, and how chemotherapy agents are combined. Patient characteristics that increase the risk of CINV include female gender, younger age, previous exposure to chemotherapy, history of alcohol abstention, and presence of nausea and vomiting with prior chemotherapy.⁶ Because 5-HT₃ receptors are important neurotransmitters involved in CINV, drugs that inhibit these receptors are commonly used in clinical practice.

Among the various types of available anti-emetic agents, 5-HT₃ receptor antagonists have become established as the cornerstone of therapy for prevention of CINV, due to their proven efficacy and low incidence of side effects.

First-generation 5-HT₃ receptor antagonists (ondansetron, granisetron, dolasetron, and tropisetron) possess an equivalent safety and efficacy profile when used at equipotent doses.⁶⁻⁸ Palonosetron is a highly selective 5-HT₃ receptor antagonist that exhibits high 5-HT₃ receptor affinity. It differs from other drugs in this class in that the plasma half-life (~40 hours) is substantially longer and it exhibits allosteric binding and positive co-operativity. Furthermore, binding of palonosetron to 5-HT₃ receptors seems to induce internalization of receptors, thereby, facilitating long-lasting receptor inhibition and activity.

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 and granisetron. In our study, Palonosetron was given in a dose of 0.5 mg OD which was found to be more affective as compared to ondansetron 4mg thrice a day and granisetron 1mg twice a day.

In this study, only 29% patients in ondansetron cohort showed complete response as compared to 98% patients in palonosetron cohort. This was consistent with the study done by Aapro et al, and Gralla et al.^{3,9}

Also, 53% patients in granisetron cohort had complete response as compared to 98% patients in palonosetron cohort. This was consistent with the study done by Rhulmann and Herrstedt, and Saito et al.^{4,10}

A meta-analysis by Celio et al found palonosetron to be statistically superior to other 5-HT₃ receptor antagonists during the delayed phase of nausea & vomiting.¹¹ Even though previous studies have shown that all 5-HT₃ receptor antagonists are equally effective and safe for the prevention of acute CINV for chemotherapy regimens, NCCN (National Comprehensive Cancer Network) updated its practice guidelines by listing palonosetron as the “preferred” 5-HT₃ receptor antagonist for the prevention of CINV associated with HEC.¹² Another valuable study stated that, in comparison to a first generation 5-HT₃ receptor antagonist palonosetron demonstrated efficacy in the prevention of delayed CINV associated with HEC.¹

CONCLUSION

Cisplatin based combination chemotherapy, used in the study are highly emetogenic chemotherapeutic agents (HEC). Poor control of acute CINV (chemotherapy induced nausea and vomiting) is an established predictor for delayed CINV that typically peaks in severity between day 2 and day 4 post-chemotherapy. Thus, this study was

conducted to compare the efficacy of 5-HT₃ receptor antagonists in preventing delayed CINV and it showed palonosetron (98% CR) to be far more effective than ondansetron (29% CR) and granisetron (53% CR). As our study was conducted in only a handful of patients and compared palonosetron against only two 5-HT₃ receptor antagonists, so a larger study including various 5-HT₃ receptor antagonists is suggested to establish the efficacy and better response of palonosetron.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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