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Original Research Paper

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

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Introduction-

Chemotherapy-induced nausea and vomiting (CINV) remains a potentially severe and distressing adverse effect of cancer treatment. The CINV risk also depends on patient characteristics, such as gender, age, and history of alcohol consumption. It has been reported that female patients are at greater risk of CINV[1].

Nausea and vomiting can also result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of performance and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment[2], thus CINV compromises the quality of life (QOL) of the patients and reduces treatment compliance.[3]

CINV is differentiated into three categories: acute, occurring within 24 hours of initial administration of chemotherapy; delayed onset , occurring 24 hours to several days after initial treatment; and anticipatory.[4]

The emetogenic potential of the chemotherapeutic agents used is the main risk factor for the degree of CINV. Antiemetic prophylaxis is directed toward the emetogenic potential of the chemotherapy. 60% to nearly 90% of patients receiving cisplatin will experience delayed emesis if not given preventive antiemetics.[4]

Principal neuroreceptors involved in the emetic response are serotonin (5-hydroxytryptamine [5-HT3]) and dopamine receptors[2] The development of the 5-HT3-receptor antagonists (5-HT3RAs) in the early 1990s was one of the most significant advances in the chemotherapy of cancer patients.[4] Palonosetron is a 5-HT3 antagonist with approximately a 100-fold higher binding affinity for the 5-HT3 receptor compared with other serotonin antagonists. Intravenous palonosetron is superior compared to other 5 HT-3 receptor antagonist in preventing delayed emesis.[2]

In this study efficacy of oral palonosetron was compared to other 5 HT-3 receptor antagonist. The primary efficacy end point was aimed at complete Response (CR) and improving quality of life (QOL).

Material and Methods-

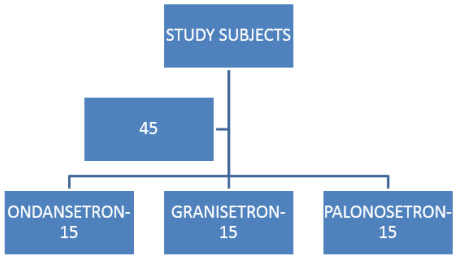
This is a prospective, observational study conducted on 45 previously untreated histopathologically-proven patients of squamous cell carcinoma of Cervix (Cx), who had attended Department of Radiotherapy, Gandhi Medical College and Hamidiya Hospital, Bhopal from January to December 2015 from. In this study the patients were selected based on our inclusion criteria which were proven cases of squamous cell carcinoma, age <70 years, do not receive other treatment, KPSS>60, normal haematological parameter, normal renal function, normal liver function . These patients were divided into three cohorts and each cohort was composed of 15 diagnosed cases of squamous cell carcinoma of Cervix

Standard protocol based chemotherapy which is highly emetogenic cisplatin based chemotherapy was administered to all of the patients. Some were given methotrexate, bleomycin and cisplatin combination and others were given paclitaxel and cisplatin. For prevention of delayed chemotherapy induced nausea and vomiting all patients were prescribed oral $5HT_3$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 to the cohort 3 from day 3 to day 7. For evaluation the patients were asked to keep a vomiting diary, interviewed on telephone and on next follow up visit. Enquiry was made about the number of episodes of nausea and vomiting experienced and how their day to day life was affected, 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 squamous cell carcinoma of cervix, receiving highly emetogenic chemotherapy were enrolled. They were divided in 3 cohorts, 15 patients received oral Ondansetron 4mg TDS (cohort-1). 15 patients received oral Granisetron 1mg BD (cohort-2) and rest 15 patients received oral Palonosetron 0.5mg OD (cohort-3) from day 3 to day 7 for prevention of delayed CINV.



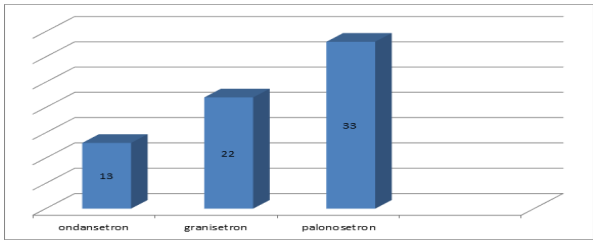
The results were analysed on the basis of response obtained from the study subjects. Patients having no complain of nausea and vomiting were graded as complete response.

Among Ondansetron cohort, on an average, 13% patients had complete response.

Among Granisetron cohort, on an average, 22% patients had

complete response.

Among Palonosetron cohort, on an average, 33% patient had complete response Thus, Palonosetron has better response in prevention of chemotherapy induced nausea and vomiting as compared to other 5HT3 receptor antagonists.



- 13% patients in ondanseteron cohort had complete response.
- 22% patients in graniseteron cohort had complete response.
- 33% patients in palonosetron cohort had complete response

DISCUSSION-

CINV is a complex phenomenon consisting of both acute (0–24 hours) and delayed (24–120 hours) components that may have different physiological mechanism[5].

CINV is differentiated into three categories: acute onset (mostly serotonin related), occurring within 24 hours of initial administration of chemotherapy; delayed onset (in part substance P related), occurring 24 hours to several days after initial treatment; and anticipatory, observed in patients whose emetic episodes are triggered by taste, odour sight, thoughts, or anxiety secondary to a history of poor response to antiemetic agents or inadequate antiemetic prophylaxis in the previous cycle of chemotherapy.[6]

In regard to their emetogenic potential, the chemotherapeutic agents are classified into four emetic risk groups: high (90%), moderate (30%–90%), low (10%–30%), and minimal (‹10%).[6] Trials have indicated that from 60% to nearly 90% of patients receiving cisplatin will experience delayed emesis if not given preventive antiemetics. Therefore, appropriate prophylaxis is indispensable. Hence, antiemetic prophylaxis is directed toward the emetogenic potential of the chemotherapy. Patient-related risk factors, including young age, a history of low alcohol intake, experience of emesis during pregnancy, impaired quality of life, and previous experience with chemotherapy, are known to increase the risk for CINV.

Previously, antiemetic therapy for CINV consisted solely of corticosteroids, with a rate of successful acute CINV control of ~30%[7]. The CINV control rate increased to ~70% with the advent of first-generation 5-HT3 RA medications [8]. The first-generation 5-HT3 RAs proved to be effective in the control of acute nausea and vomiting; however, a proportion of patients suffer delayed nausea and vomiting, which constitutes a major problem in cancer chemotherapy.[3]

Effective antiemetic regimens for highly and MEC have historically been based on the combination of a 5-HT3 receptor antagonist and dexamethasone. This combination is highly effective for controlling acute emesis, but less so for delayed emesis, and the contribution of a first-generation 5-HT3 receptor antagonist to the management of delayed emesis has been questioned. The properties of palonosetron, a second-generation 5-HT3 receptor antagonist, include a prolonged half-life of approximately 40 hours and effects on receptor internalization. These properties underlie the effectiveness of this drug in the management of delayed nausea and vomiting.

Ondansetron, granisetron, and palanosetron are effective in preventing acute emesis, but seem to be less effective in preventing delayed emesis. However, intravenous palonosetron is effective for preventing both delayed and acute emesis. A meta-analysis of randomized controlled trials found that adding a 5-HT3 antagonist to dexamethasone did not improve its ability to prevent delayed emesis.[9]

The present analysis revealed a significantly higher CR rate in patients receiving single daily dose of palonosetron as compared to patients receiving ondansetron and gralisetron, in terms of treatment of delayed-onset CINV. Previous studies have focused on the use of first-generation 5-HT3 RA, while the present data suggest the potential efficacy of the second-generation 5-HT3 RA palonosetron.

This study shows that there was a significant difference between the three cohorts, with palonosetron cohort having highest response rate (33%) as compared to ondansetron cohort (13%) and granisetron cohort (22%). These results were consistent with the studies done by Aapro,et al[10] and Saito, et al[11]. However, the response rate was not much significantly different between the palonosetron cohort and granisetron cohort, as consistent with the study done by Ohzawa,et al.[12] The large difference between ondansetron cohort (13%) and palonosetron cohort (33%) was consistent with the results of studies done by Grala,et al[113] and Aapro,et al[10].

Conclusion:

Carcinoma cervix constitute a significant proportion of the patient population in which chemotherapy is commonly indicated. The adjuvant chemotherapies for carcinoma cervix usually involve moderately to highly emetogenic agents and regimens. Since most of the chemotherapy regimens for carcinoma cervix are of moderate emetogenic potential, optimization of an antiemetic regimen would significantly improve QOL 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. In this study, oral palonosetron at a dose of 0.5 mg OD was found to have better response as compared to other 5HT-3 receptor antagonist. The evaluation of vomiting and nausea is difficult; however, the evaluation of complete response was possible via the use of patients log and survey.

REFERENCES-

[1] Satoe Fujiwara, Yoshito Terai, Satoshi Tsunetoh, Hiroshi Sasaki, Masanori Kanemura, Masahide Ohmichi, Palonosetron versus granisetron in combination with aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with gynecologic cancer, J Gynecol Oncol Vol. 26, No. 4:311-319.

[2] David S. Ettinger, MD; Debra K. Armstrong, RN; Sally Barbour, PharmD, BCOP; Michael J. Berger, PharmD, BCOP; Philip J. Bierman, MD, et al, Antiemesis -Clinical Practice Guidelines in Oncology Journal of the National Comprehensive Cancer Network | Volume 7 Number 5 | May 2009, 572-595.

[3] Eriko Takatori, Tadahiro Shoji, Yuki Miura, Miyuki Nagao, Anna Takada, Takayuki Nagasawa, A phase II clinical trial of Palonosetron for the management of delayed vomiting in gynecological cancer patients receiving paclitaxel/carboplatin therapy, Molecular and clinical oncology 3: 281-286, 2015.

[4] Karin Jordan, Christoph Sippel, Hans-Joachim Schmoll, Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations, *The Oncologist* 2007;12:1143–1150.

[5] Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl JMed 2008;358:2482-94.

[6] Karin Jordan, Christoph Sippel, Hans-Joachim Schmoll, Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations, *The Oncologist* 2007;12:1143–1150.

[7] Ioannidis JP, Hesketh PJ and Lau J: Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol 18: 3409-3422, 2000.

[8] Olver I, Paska W, Depierre A, Seitz JF, Stewart DJ, Goedhals L, McQuade B, McRae J and Wilkinson JR: A multicentre, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. Ondansetron Delayed Emesis Study Group. Ann Oncol 7: 945-952, 1996.

[9] Huang JQ, Zheng GF, Deuson R, et al. Do 5-hydroxytryptamine3 receptor antagonists (5-HT3) improve the antiemetic effect of dexamethasone for preventing delayed chemotherapy-induced nausea and vomiting (CINV)? A meta-analysis of randomized controlled trials [Abstract]. J Clin Oncol 2004;22:Abstract 6037.

[10] Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA, Bertoli LF, Yunus F, Morrica B, Lordick F and Macciocchi A: A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 17: 1441-1449, 2006.

[11] Saito M, Aogi K, Sekine I, Yoshizawa H, Yanagita Y, Sakai H, Inoue K, Kitagawa C, Ogura T and Mitsuhashi S: Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomized, comparative phase III trial. Lancet Oncol

10: 115-124, 2009.
[12] Ohzawa H, Miki A, Hozumi Y, Miyazaki C, Sagara Y, Tanaka Y, et al. Comparison between the antiemetic effects of palonosetron and granisetron in breast cancer patients treated with anthracyclinebased
regimens. Oncol Lett 2015;9:119-24.
[13] Gralla R, Lichinitser M, Van der Vegt S, Sleeboom H, Mezger J, Peschel C,et al: Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 14: 1570-1577, 2003.