

Comparative Study of Ondansetron Verses Palonosetron in Cisplatin Induced Nausea Vomiting

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Abstract

Objective: Nausea and vomiting can adversely affect the life of a patient with cancer both during and after chemotherapy. A common side effect of Cisplatin regimens is severe nausea and vomiting. Cisplatin based regimens for cancer is categorized as highly emetogenic chemotherapy. There is considerable progress in the control of nausea and vomiting from those early days but there is still paucity of data on antiemetic regimens for patients undergoing multiday Cisplatin based regimens. Palonosetron differs from first-generation 5HT₃ antagonists. It has a longer half-life and a 100-times greater binding affinity to the 5HT₃ receptor. This prospective study was designed to compare the efficacy of antiemetics Ondansetron and Palonosetron to prevent Chemotherapy induced nausea vomiting (CINV) in cancer patients on Cisplatin regimens. **Material and Methods:** A prospective randomised study was conducted at the department of Oncology at a tertiary care centre. A total of 40 chemotherapy naïve patients were enrolled in the study; 20 each in the ondansetron and palonosetron groups. All patients received Cisplatin in a dose of at least 50 mg /sq meter of body-surface area. The severity of nausea was recorded and vomiting was recorded in terms of number, frequency and time to rescue medication. **Results:** Of 40 patients with cancer placed on chemotherapeutic regimens containing Cisplatin 20 were placed in the Ondansetron arm and 20 were placed in the Palonosetron arm. Mean age in Ondansetron group was 54±13.84 and in Palonosetron group was 56±11.93. Out of 20 patients in ondansetron group mean vomiting was 6.4 times while in Palonosetron it was 4.2. In Ondansetron group 14 (70%) showed response to Ondansetron while in Palonosetron 16 (80%) showed response. There was no response to treatment in 6 (30%) in Ondansetron and 4 (20%) in Palonosetron. Palonosetron given daily from Day 1 up to Day 5 of chemotherapy significantly reduced the incidence of nausea on. **Conclusion:** The overall complete response (CR) rates of Palonosetron were slightly higher than the Ondansetron. Palonosetron can reduced the incidence and severity of nausea and vomiting who are on Cisplatin therapy as compared to Ondansetron.

Introduction

Chemotherapy induced nausea and vomiting can adversely affect patients' quality of life, cause electrolyte imbalances and dehydration, increase healthcare costs, and could lead to delays in treatment or patient refusal of further treatment.^[1] A common side effect of Cisplatin regimens is severe nausea and vomiting. It is categorized as highly emetogenic chemotherapy with patients being vulnerable to nausea and vomiting.^[2] These symptoms are debilitating for patients. There is considerable progress in the control of nausea and vomiting from those early days but there is still a paucity of data on antiemetic regimens for patients undergoing multiday Cisplatin combination. Different pathways are there in the body that induce emesis. Each relying on a set of different neurotransmitters, including serotonin, dopamine, histamine, and substance P.^[3] Cisplatin damages the gastrointestinal tract and in turn causes calcium dependent exocytic release of 5-hydroxytryptamine (HT)₃ from enterochromaffin cells of the GI mucosa. Released 5-HT₃ binds to its receptors on the vagal afferent neurons and this binding activates the chemoreceptor trigger zone and vomiting centre. When chemoreceptor trigger zone is activated, it releases various neurotransmitters which in turn stimulate the vomiting centre. Once vomiting centre is activated, it modulates efferent transmission to respiratory,

vasomotor, and salivary centres as well as to abdominal muscles, diaphragm, and oesophagus, resulting in emesis.^[4]

Metoclopramide, was widely used in Europe for decades for prevention of motion sickness but it was considered ineffective against chemotherapy induced nausea. In 1980s, it was discovered that massive doses of the drug (2 mg/kg given before and after chemotherapy) helped to minimize nausea and vomiting in most patients treated with Cisplatin. But the higher doses was associated with Parkinsonian symptoms which were somewhat dissipated with addition of diphenhydramine. CINV prophylaxis with combination of dexamethasone and metoclopramide was the mainstay of treatment in the 1980s till introduction of ondansetron.^[5] In 1990s 5-hydroxytryptophan receptor type-3 (5HT₃) antagonists, ondansetron, granisetron, and dolasetron was introduced which changed the management of Chemotherapy induced nausea vomiting (CINV) for patients receiving chemotherapy with high or moderate emetogenic potential.^[6] A novel neurokinin-1 (NK1) receptor antagonist, and palonosetron, a second-generation 5HT₃ antagonist was introduced in 2003.^[7,8] With the introduction of neurokinin 1 receptor antagonist (NK1RA) as an antiemetic prophylaxis, additional improvement in CINV control was observed, and as a testimony, it was considered as an essential drug in the prophylaxis regimen in all the major international guidelines such as American Society of Clinical

Oncology, National Comprehensive Cancer Network, and Multinational Association of Supportive Care in Cancer (MASCC).^[4,6] The addition of dexamethasone to 5HT3 antagonists provides further protection against acute and delayed CINV.^[8] Palonosetron differs from first-generation 5HT3 antagonists. It has a longer half-life (around 40 hours as compared to 3-9 hours with other 5HT3 antagonists) and a 100-times more greater binding affinity to the 5HT3 receptor.^[12,13,14]

This prospective study was done to compare the effect of Ondansetron and Palonosetron on patients receiving cisplatin to prevent CINV in patients with cancer.

Material and Methods

This prospective, open label study was carried out in the department of Oncology at a tertiary care centre over a 4 month period. Informed consent prior to study enrolment was obtained from all the patients. Patients included were in the age group of 48 to 86 years scheduled to receive the first dose of their first cycle of cisplatin. Patients were required to be new to chemotherapy or treated with only low or minimally emetogenic chemotherapy in the past. Exclusion criteria was any vomiting or retching within 24 hours before administration of the study medications; administration of an antiemetic within 24 hours before study medication administration, excluding the use of benzodiazepines; grade 2 nausea or greater. Also patients were excluded if they had evidence of uncontrolled cardiovascular or cerebrovascular disease, or uncontrolled nausea and vomiting due to other organic causes. The pre-treatment evaluation was done which consist of a complete history and physical examination, electrocardiographic assessment, a complete blood count with differential, and a serum biochemistry profile. Laboratory tests were repeated 24 hours after administration of the study drug.

All patients received cisplatin in a dose of at least 50 mg /sqmeter of body-surface area, dissolved in 500 ml of 5 percent dextrose in 0.45 percent sodium chloride and administered as a 60-minute intravenous infusion.

Patients randomized to the ondansetron group who received ondansetron 24 mg once orally on day 1, 30 min prior to chemotherapy. Patients randomized to the palonosetron group received palonosetron 0.25 mg IV once on day 1, 30 min prior to chemotherapy. Patients were given a medication calendar and were counselled regarding the appropriate home medication administration. Antiemetic-rescue treatment was administered if patients experienced three episodes of emesis in one hour,

A total of 40 patients were enrolled of which 20 were enrolled in the Ondansetron arm and 20 were enrolled in the palonosetron arm. Efficacy endpoints included emesis, intensity of nausea and its interference with patient functioning, and rescue antiemetic use. Patients were continuously monitored for nausea and emesis throughout the 24-hour study period by an observer who recorded the number, time, and intensity of each episode of emesis.

Statistical analysis was done by to compare the ondansetron and palonosetron groups. P value below 0.05 was considered to indicate statistical significance. Means and standard deviations (SD) were used to describe continuous variables while frequencies and proportions described categorical variables.

Observation and Results

A total of 40 patients with cancer were placed on chemotherapeutic regimens containing cisplatin were included in the study of which 20 were placed in the Ondansetron arm and 20 were placed in the palonosetron arm

Table 1: Demographic characteristics

variable	Ondansetron group	Palonosetron group	P value
No of patients	20	20	-
Age (mean/SD)	54±13.84	56±11.93	P = 0.6273
Sex(Male/Female)	12/8	14/6	-
Type of cancer			
Lung	02	3	P = 0.6369
Head and neck	06	7	P = 0.7389
Genitourinary	10	8	P = 0.5302
Others	02	2	P = 0.3819

20 patients each were put in Ondansetron group and palonosetron group. Mean age in Ondansetron group was 54±13.84 and in palonosetron group was 56±11.93. Male patients in ondansetron group were 12 while female patients were 8. Male patients in palonosetron group were 14 while female patients were 6. Two patients in ondansetron group had lung cancer, six had head and neck neoplasia, ten had genitourinary cancer while 2 patients were placed in others group. In palonosetron group patients with lung, head& neck genitourinary and others cancers were 3, 7, 8 and 2 respectively.

Table 2: characteristics of cisplatin-induced vomiting

Variable	Ondansetron group	Palonosetron group	P value
No of patients	20	20	
Mean No of episodes in 24 hours	6.4	4.2	P < 0.0001
Response	14 (70%)	16 (80%)	P = 0.4708
Complete	6 (30%)	9 (45%)	P = 0.3333
Partial	8 (40%)	7 (35%)	P = 0.7471
No response	6 (30%)	4 (20%)	P = 0.4708

Out of 20 patients in ondansetron group mean vomiting was 6.4 times while in Palonosetron it was 4.2. In ondansetron group 14 (70%) showed response to ondansetron while in Palonosetron 16 (80%) showed response. There was no response to treatment in 6 (30%) in ondansetron and 4 (20%) in Palonosetron. Palonosetron given daily from Day 1 up to Day 5 of chemotherapy significantly reduced the incidence of nausea.

Discussion and Conclusion

Prior to the advent of 5HT3 receptor antagonists, patients were often unable to complete chemotherapy regimens due to profound nausea or vomiting. CINV is frequent in patients with malignancies and who are receiving chemotherapy. Currently antiemetic regimen

includes a 5-HT₃ receptor antagonist in combination with an NK1 receptor antagonist and dexamethasone and palonosetron is the preferred 5HT₃ receptor antagonist for HEC.^[15,16]

No statistically significant differences were detected in both the regimes. These data can be used for further studies. The overall complete response rate in our study for ondansetron was 6 (30%) and for Palonosetron was 9 (45%). In a study by Einhorn et al. they evaluated that palonosetron 0.25 mg intravenous given on chemotherapy days 1, 3, and 5 plus dexamethasone in patients receiving multiday cisplatin chemotherapy for germ cell tumour. Majority of patients had no vomiting at any time throughout days 1-5 (51%) or days 6-9 (83%), had no moderate or severe nausea, and also they did not require rescue medication.^[17] In one study Complete response (CR) rate, which was defined as no vomiting and no rescue medication use, was achieved in 90% of the patients in the first chemotherapy course, and high CR rates were also observed in the second and third courses.^[18]

In a study by Musso et al demonstrated that 80% of the patients who received palonosetron did not develop CINV as compared to 60% of patients who received Ondansetron.^[19]

In conclusion, palonosetron can reduced the incidence and severity of nausea and vomiting who are on Cisplatin therapy as compared to Ondansetron. But there are some limitations to this study this study was having very small sample size and bigger number of patients are required to prove the efficacy of the drug. The overall CR rates of palonosetron was slightly higher than the Ondansetron, these data may demonstrate consistent numerically higher rates of CR and lower rates of vomiting and retching in the palonosetron-containing group.

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