A comparative study of Ondansetron and Palonosetron in the control of cisplatin induced emesis

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Abstract
Chemotherapy induced nausea and vomiting (CINV) is one of the most undesirable treatment-related side effects among cancer patients. The antiemetic class of drugs which are very effective for the prevention and treatment of CINV is Selective 5-hydroxytryptamine (5-HT3) receptor antagonists. This randomized study compared the efficacy and safety of a single, intravenous dose of Palonosetron with daily intravenous doses of Ondansetron in the prevention of acute and delayed CINV in patients receiving highly emetogenic multiple-day cisplatin therapy in the Department of Oncology and Obstetrics and Gynaecology, Tertiary care hospital, Coimbatore, Tamilnadu. Patients treated with Palonosetron exhibited higher complete response rates, better control and prolonged protection of nausea and emetic episodes, less use of rescue medications and less impact on patients’ quality of life. Thus, Single fixed dose of Palonosetron is more effective than multiple doses of Ondansetron.

Keywords: Antiemetic, Palonosetron, Ondansetron, complete response, nausea

Introduction
In cancer therapy, one of the most prevalent and unbearable treatment-related side effects is chemotherapy induced nausea and vomiting (CINV) [1]. CINV may cause dehydration, poor nutrition or electrolyte disturbances. It can also affect the quality of life of the patients, their desire to continue cancer therapy, and ultimately their survival [2]. The emetogenic potential, schedule, dose, route, and rate of drug administration are the treatment related risk factors. Cisplatin, an alkylating agent is classified as highly emetogenic agent [3,4]. In multiple-day chemotherapy, as there is overlapping between acute and delayed vomiting from the first day till the last day of chemotherapy, it is not easy to prescribe a specific antiemetic regimen each day for prophylaxis [5]. There was a significant improvement in the prevention and treatment of acute CINV with the introduction of 5-HT3 receptor antagonists like Ondansetron combined with dexamethasone (corticosteroid). However, the control of delayed CINV still remains a challenge and administering multiple doses of 5-HT3 receptor antagonists, 24 hours after administration of chemotherapy for delayed emesis was not effective [3]. Palonosetron is a selective, highly potent, second-generation 5-HT3 receptor antagonist with plasma elimination half-life ~40 hours. Its binding affinity to the 5-HT3 receptor is higher (approximately 100-fold) than other 5-HT3 receptor antagonists [6]. In patients receiving moderate to highly emetogenic agents, the only 5-HT3 receptor antagonist that has any effect in the prevention of delayed CINV is Palonosetron [7]. Thus the present study was conducted to compare the efficacy and safety of a single, intravenous dose of Palonosetron with daily intravenous doses of Ondansetron in the prevention of acute and delayed CINV in patients receiving highly emetogenic multiple-day cisplatin therapy.

Materials and Method
The study was conducted according to the Declaration of Helsinki and approval was obtained from the Institutional Ethics Committee. Written informed consent was obtained in local vernacular language from every patient before enrolment.

Patient Selection
Patients aged >18 years and <80 years with clinically, histologically or cytologically proven malignancies, who are naïve to chemotherapy, but scheduled to receive Cisplatin ≥50 mg/m² for 3 days, with a Karnofsky performance status ≥60% were eligible for the study. Patients...
were excluded if they were scheduled to receive chemotherapy with highly emetogenic agent other than Cisplatin during study days 1 - 7 or radiotherapy of upper abdomen / cranium during study days 1 - 7, with history of severe, uncontrolled concurrent illness, history of emesis or retching or nausea (grade ≥2) <24 hours before chemotherapy, history of GI obstruction, ascites, or ongoing emesis due to any organic etiology, history of convulsions, uncontrolled pleural effusion, cardiovascular dysfunction, symptomatic hepatic or renal impairment and with known hypersensitivity to study drugs or to other selective 5-HT3 antagonists.

Study Design
This was a open labelled, randomized, prospective, comparative, Interventional parallel group study conducted in the Department of Oncology and Department of Obstetrics and Gynaecology in Tertiary care hospital, Coimbatore, Tamil Nadu. Eligible patients were randomized using computer generated random table to receive single dose of Palonosetron 0.25mg intravenously over 30 seconds, 30 minutes prior to the initiation of chemotherapy on day 1 of cisplatin treatment or Ondansetron 8mg intravenously 30 minutes prior to the initiation of chemotherapy daily from day 1 through day 3 of cisplatin treatment. Dexamethasone (prophylactic corticosteroid) 16mg intravenously 15 min before chemotherapy was allowed in both the groups daily from day 1 to day 3. All the subjects who were administered cisplatin (≥50 mg/m²) infusion for three days were followed for a total of seven days (from day 1 to day 7), starting from the first day of chemotherapy. The chemotherapy days (day 1 to day 3) was considered as acute phase, whereas the period of post chemotherapy (day 4 to day 7) was considered as delayed phase. The period from Day 1 to Day 7 was considered as overall phase. The subjects were instructed to use the diary cards to record the occurrence of emetic episodes, use of rescue medications and grade of nausea.

Follow UP
Follow up was done on day 2 (approximately 24 hours after the administration of chemotherapy) and once between day – day 7. Patients were enquired about adverse events and use of concomitant medications through day 7.

Efficacy Parameters
Primary Endpoint
• Proportion of patients with Complete response (no emetic episodes, no rescue medications) during the acute (day 1 to day 3), delayed (day 4 to day 7) and overall phases (day 1 to day 7).

Secondary Endpoints
• Proportion of patients without nausea or with mild nausea
• Absence of emesis/Number of emetic episodes
• Time to first emetic episode
• Use of rescue medication
• Time to first administration of rescue medication
• Impact of chemotherapy induced nausea & vomiting on daily activities

Statistical Analysis
Statistical analysis was performed with the help of the statistical package SPSS 17. Baseline characteristics were tabulated by descriptive statistics (mean, standard deviation) and frequency table. Intention-to-treat hypothesis was followed in this study. Complete response rates, proportion of patients without or with mild nausea, with no emesis, rescue medication use, and with no impact on daily living were analyzed using chi-square test. Between group differences for these parameters was done using T test, two-sided Fisher’s exact test and Pearson chi-square test. Kaplan-Meier and log rank tests were used to compare the time to first emetic episode and time to first administration of rescue medication. Adverse events were expressed in percentages. To compare two groups, p value ≤0.05 in two-sided test was considered as significant.

Patient Disposition: Consort Diagram
Results
Of 108 patients assessed for eligibility, 105 were randomized to receive either Palonosetron 0.25mg (n=53) or Ondansetron 8mg (n=52). Of these, 52 patients completed the study in each group. One patient was withdrawn from the Palonosetron group before the administration of the study drug.

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Parameters</th>
<th>Palonosetron</th>
<th>Ondansetron</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) yrs</td>
<td>55.3±8.7</td>
<td>54.7±11</td>
<td>0.745</td>
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<tr>
<td>Gender n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (35)</td>
<td>19 (36)</td>
<td>0.838</td>
</tr>
<tr>
<td>Female</td>
<td>34 (65)</td>
<td>33 (64)</td>
<td></td>
</tr>
<tr>
<td>KPS (mean ± SD)</td>
<td>75.3±9.5</td>
<td>75.7±11</td>
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<tr>
<td>Tumor Type</td>
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<td>cancer head and neck</td>
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<td>cancer cervix</td>
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<td>13 (27)</td>
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<td>1 (2)</td>
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</tr>
<tr>
<td>cancer penis</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>cancer pancreas</td>
<td>0 (0)</td>
<td>1 (2)</td>
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</table>

There were no significant differences in the baseline characteristics between the treatment groups.

Primary Efficacy Parameter

As shown in Table 2, complete response rates (CR) are higher in the Palonosetron group during the acute (p = 0.153), delayed (p = 0.005) and overall phases (p = 0.04) compared to the Ondansetron group (Figure 2).

Secondary Efficacy Parameters

The proportions of patients with no or mild nausea on each study day are shown in Table 3. On Day 1, >80% of the patients in either group had no or mild nausea. The proportion of patients with no or mild nausea declined similarly on day 2 and day 3 in either group. From Day 4 to Day 7, significantly more patients in the Palonosetron group reported no or mild nausea than in the Ondansetron group (P< 0.05).

Table 5: Time to 1st emetic episode and time to first administration of rescue medication

As shown in table 5, the median time to first emetic episode was significantly longer for patients receiving Palonosetron when compared to the patients receiving Ondansetron. With the help of log-rank test, the differences between the groups were found to be significant (P = 0.008).
The Kaplan-Meier plot for the time to first emetic episode of the study drugs are shown in Figure 1. Similarly the median time to rescue medication was longer in the Palonosetron group than that of the Ondansetron group. ($p = 0.431$)

As shown in Figure 2, significantly more patients who received Ondansetron required rescue medication, than those who received Palonosetron. ($p = 0.031$; statistically significant)

$P < 0.05$; statistically significant

**Fig 1:** Kaplan-meier curve for time to first emetic episode

**Fig 2:** Proportion of patients who used rescue medication overall

**Fig 3:** Proportion of patients with no or little impact of CINV on daily living by study day are shown
The percentage of patients who reported no or less impact on daily living (NIDL) (score >6 on seven-point FLIE scale) was higher for Palonosetron group than for Ondansetron group in both acute and delayed phases. As shown in Figure 3, the significant differences were seen on all days. \((P < 0.05)\)

**Adverse Events**

No patient was withdrawn from the study due to adverse event related to the study drugs. No serious adverse event was reported in either group. The most common adverse events were constipation (Palonosetron, 15% of patients; Ondansetron, 10% of patients) followed by headache (Palonosetron, 5% of patients; Ondansetron, 4% of patients). There were no significant differences in adverse events between the groups. No significant changes were seen in vital signs, laboratory tests, and electrocardiogram in either group.

**Discussion**

The introduction of Ondansetron, the first 5-HT3 antagonist for chemotherapy induced nausea and vomiting, was a milestone in antiemetic therapy. Though significant improvements have been made in the management of acute CINV, delayed CINV continues to be a problem, as it was thought to have a separate mechanism. One of the factors in the development of delayed nausea and vomiting is poor control of acute nausea and vomiting. Most of the studies have been investigated in single day chemotherapy with cisplatin or anthracycline/cyclophosphamide regimens. There is paucity of information in the setting of multi-day chemotherapy. Patients can develop emesis from numerous diverse mechanisms, like acute, delayed and/or anticipatory nausea and vomiting, thus representing complexity in the mechanism of emesis. In a study conducted by baltzer and colleagues in patients undergoing 5-days cisplatin therapy, Ondansetron plus dexamethasone was given daily as prophylactic antiemetic agents. Fifty-eight percent reported no emesis during the chemotherapy days. However, three or more emetic episodes were reported by 25%, 27%, and 29% on days 3-5. Thus for the effective control of delayed nausea and vomiting, a 5-HT3 receptor antagonist with longer duration of action should be used.

Our study was to compare the efficacy and safety of Palonosetron with Ondansetron in the prevention of acute and delayed chemotherapy-induced nausea and vomiting following multiple-day cisplatin therapy. In our study, we included patients with clinically or pathologically proven malignancies, who are scheduled to receive first cycle of cisplatin chemotherapy for three days. The chemotherapeutic agent used in our study is cisplatin. Among the highly emetogenic agents, cisplatin has been commonly used in many studies as it has great potential to induce delayed emesis. We did not allow heterogeneity of chemotherapy regimens among study population, as the patterns and intensities of emesis may vary in different regimens and delayed emesis is not extensively studied for some drugs or regimens. We have included only chemotherapy naïve patients so as to avoid the bias of anticipatory nausea and vomiting. The mean age of the subjects in our study was 55 years. Majority of the study subjects were females (64%) in our study. Female gender is one of the important predictors for the development of CINV. The doses of the study drugs were based on the antiemetic guidelines from the European Society for Medical Oncology, the Multinational Association Of Supportive Care in Cancer, American Society of Clinical Oncology, and the National Comprehensive Cancer Network.

In our study, higher complete response rates were reported by the patients in the Palonosetron group when compared to those in the Ondansetron group during the acute, delayed and overall phases (p = 0.153; 0.005; and 0.004; respectively). This result is similar to those reported by Gralla et al. and tended to be better than those in the study of Aapro et al, who reported complete response of acute emesis in 64.7% of patients in the Palonosetron group and 55.8% of patients in the Ondansetron group, respectively. In our study, patients who received Palonosetron achieved high degree of nausea control compared to those who received Ondansetron. More patients treated with Palonosetron experienced no nausea or mild nausea than those treated with Ondansetron during the acute (96% versus 78%), delayed (71% versus 30%) and overall phases (71% versus 28%). Similarly, absence of emesis was reported by greater proportion of patients who received Palonosetron than those who received Ondansetron during the acute (84% versus 73%), delayed (55% versus 28%) and overall phases (51% versus 25%). Statistical significance was seen in the delayed and overall phases for the above parameters. \((P < 0.05)\)

In our study patients in the Palonosetron group had longer time to first emetic episode (p = 0.008) and time to rescue medication (p = 0.431) than that of Ondansetron group. It was similar to the study conducted by Aapro et al and Gralla et al. The median time to first emetic episode was 74 hours in Palonosetron group compared to 70 hours in the Ondansetron group. The median time to rescue medication was 94 hours in the Palonosetron group versus 84 hours in Ondansetron group. The use of rescue medication was observed in greater proportion of the patients in the Ondansetron group when compared to that of Palonosetron group (p = 0.031).

Only few trials have investigated the impact of chemotherapy induced nausea and vomiting on patients’ quality of life. The results from our FLIE evaluations have shown that a 67% of the patients in the Palonosetron group have reported NIDL during the overall phase, whereas it was 50% in the Ondansetron group, with differences being statistically significant. NIDL was reported by 75% and 84% of patients in the Palonosetron group in the acute and delayed phases respectively, whereas in the Ondansetron group 51% and 57% of patients reported NIDL during the acute and delayed phases respectively \((P < 0.05)\). Results from other trials have documented that significantly more patients in the Ondansetron group (70% - 73%) reported NIDL, than the patients in the Ondansetron group (59% – 64%) during the acute and delayed phases. Interestingly, patients attaining complete response rates were tended to experience a decreased impact of CINV on activities of daily life, and vice versa. One study in particular demonstrated in patients undergoing moderate or highly emetogenic chemotherapy that delayed nausea had a negative impact on activities of daily living in 75% of the patients based upon the FLIE evaluations. Both Palonosetron and Ondansetron were well tolerated and had similar incidence and pattern of adverse events. Most of the adverse events were mild and unlikely or unrelated to the study drugs. Constipation and headache were the most frequent adverse events in both the groups as has been shown by Aapro et al and Eisenberg et al. No significant changes were recorded in vital signs, laboratory
investigations, and Electrocardiogram. No safety concerns were raised in this study. From the above results it was proved that patients treated with single intravenous dose of Palonosetron 0.25mg on first day of 3-day cisplatin therapy, combined with dexamethasone (on three consecutive days beginning on day 1) as prophylactic antiemetic therapy exhibited higher complete response rates, better control and prolonged protection of nausea and emetic episodes and less use of rescue medications. It was safe and well tolerated. Therefore, Palonosetron was found to be superior to Ondansetron in preventing acute and delayed nausea and vomiting following multiple day cisplatin based chemotherapy; and it would be a significant and important addition to antiemetic therapy in these settings.

Conclusion
Based on the results of our study, we conclude that Single fixed dose of Palonosetron administered with dexamethasone is more effective than multiple doses of Ondansetron with dexamethasone in preventing acute and delayed chemotherapy-induced nausea and vomiting following highly emetogenic multiple day chemotherapy.

References
2. ASHP Commission on Therapeutics. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm. 1999; 56:729-64.