Does a single dose of Palonosetron have any role in preventing chemotherapy-induced nausea and vomiting in pediatric patients? A double-blind, randomized controlled trial.

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Abstract

Objectives: Chemotherapy-induced nausea vomiting (CINV) is a troublesome side-effect of chemotherapy in pediatric patients undergoing Osteosarcoma treatment. The role of 5HT3 antagonists needs to be explored for the same. The study aims to evaluate the superiority of single-dose Palonosetron over Granisetron in pediatric patients undergoing moderate emetogenic therapy for osteosarcoma. Materials and Methods: In this double-blind, case-controlled, randomized study, pediatric patients were assessed for acute nausea and vomiting following moderate emetogenic chemotherapy for osteosarcoma. These children were assigned to group I (palonosetron) and group II (Granisetron) without other antiemetic prophylaxis. The primary objective variable was children's segment with complete response during the acute phase of the first on-study chemotherapy cycle. Risk factors associated with the trial were analyzed. The patients were followed for the first 24 hours following chemotherapy. Results: A total number of 200 children were evaluated, and other factors which might alter the response were assessed into two groups. These 200 children underwent 604 blocks of chemotherapy. The complete responses (CR) were documented in 83% and 72% receiving palonosetron and Granisetron, respectively, during the acute phase. The only dexamethasone, used as rescue medication, was found to be a significant risk factor that predisposed the response ($p<0.05$) Conclusion: Palonosetron is an effective alternative to Granisetron as a single dose for preventing CINV in children receiving MEC for osteosarcoma.

INTRODUCTION

Cancer is tormenting and devastating, but with the incessant emergence of medical brilliance, chemotherapy is launched as one of the reassuring measures. The advent of chemotherapy combined with radiotherapy and surgery reinstated the hope for survival. However, along with it came a profusion of anguishing side effects. Side-effects of chemotherapy are nephrotoxicity, neurotoxicity, ototoxicity, myelosuppression, nausea, and vomiting. Among them, nausea and vomiting are annoying, especially for children, leading to a compromised quality of life post-chemotherapy. Delayed emesis is also one of the reasons adolescents and children disagree with further treatment.[1,2]

According to emetogenic classification of Pediatric Oncologic group of Ontario3 (POGO), August 2013; various drugs were classified as highly emetogenic drugs (carboplatin, cisplatin, cyclophosphamide, methotrexate, doxorubicin) and moderately emetogenic drugs (epirubicin and ifosfamide), which are commonly used for

Osteosarcomas's chemotherapy in children. Moreover, even with the best antiemetic regimes, nausea and vomiting continue to be the most irksome aftermath of chemotherapy in children3.

Cisplatin or doxorubicin-induced emesis was predominant before the 1980s. In the 1990s, a combination of a corticosteroid and a 5-HT_3 receptor antagonist became a customary practice. High dose metoclopramide and Dexamethasone (Allan et al., 1984)[4] proved to be effectual to a certain degree. However, specific adverse effects, especially extrapyramidal reactions, commonly found in children and adolescents, have curbed high dose metoclopramide use.

5-hydroxytryptamine 3 (5-HT3) receptor antagonists are now gold standard for chemotherapy-induced nausea and vomiting (CINV) prevention therapy since emesis is triggered by activation of 5-HT3 receptors by serotonin released from enterochromaffin cells in the small intestine, located on vagal afferents[5,6]. The effectiveness of the first generation 5-HT3-receptor antagonists ranges from 50% to 70% in preventing acute chemotherapy induced nausea and vomiting (CINV)[3]. Although, there was significant improvement in the drug therapy for the treatment of the CINV, about fifty percent of the patients have significant amount of acute and delayed CINV following moderate or highly emetogenic chemotherapy[7,8]. So, there is an ample scope of research in the field of controlling CINV.

The combination of dexamethasone[10-14] with first-generation 5-HT3-receptor antagonists is effective against the acute CINV, however, the second generation 5-HT3-receptor antagonist, palonosetron, is a dynamic, extremely selective, and having intense receptor binding capacity along with prolonged plasma half life (40 hr), is quite potent as a single dose in preventing both acute and delayed CINV related to moderate and highly emetogenic chemotherapy[9-13]. However, very few studies have been done so far to establish the single-dose palonosetron efficacy over the combination of the drug therapy to control CINV in patients undergoing moderate emetogenic therapy (MEC) [9, 14-16].

No standard paediatric antiemetic treatment has yet been implemented, considering all the advancements and the inclusion of newer and improved medication regimens in the treatment of chemotherapy-induced nausea and vomiting. This research was carried out on this unique population prone to nausea and vomiting and on the need to assess the effectiveness and side effects of antiemetics.

The goal of this study was to compare the incidence of chemotherapy-induced nausea and vomiting in paediatric patients who received moderately emetogenic Osteosarcoma chemotherapy by comparing Granisetron with palonosetron. The research primarily focused on estimating the frequency of CINV in the two groups.

Materials and Methods

Patient recruitment and Selection:

To fulfill the research objective, the authors planned and executed a randomized controlled, double-blind clinical trial which was performed at the Department of Paediatrics, Chengdu University. The study was approved by the institutional review board and the local ethical committee (protocol CU # RC/IRB/2016/1042). The study followed the benchmark set by the Declaration of Helsinki. All patients without systemic complications who strictly satisfied the inclusion criteria were included.

This study enrolled consecutive children with osteosarcoma, <18 years of age, but not below 3 years of age, receiving moderate emetogenic chemotherapy in the outpatient (daycare) or inpatient settings from August 2016 to August 2019.

The following exclusion criteria were followed:

Children with abnormal Liver function test (LFT) or Renal function test (RFT) or those with organic disorders likely to cause vomiting, Children who were on concurrent radiotherapy or received radiotherapy within the study period of one week, patients who were on antiemetic therapy within first 24 hours of recruitment, known hypersensitivity towards any study drug, other associated adverse effects of chemotherapy. Furthermore, the anticipatory vomiting could create confusion in the results; the participants were avoided

successive chemotherapy. Patients were asked to give written Informed consent before participating in the study.

The moderate emetogenic therapy regimen as suggested by the POGO Guidelines for the treatment of Osteosarcoma were used[3,14]. The regimen are as follows:

a) Epirubicin (75 mg/m2) plus iphosphamide (2,500 mg/m2)

b) Epirubicin (75 mg/m2) plus carboplatin (600 mg/m2)

c) Iphosphamide (2,500 mg/m2) plus carboplatin (600 mg/m2)

The Pediatric Oncology Group of Ontario (POGO) guidelines were followed for classifying the emetogenic potential of each chemotherapy regimen[3]. A single- or multiple-day chemotherapy was considered as one session.

Standard antiemetic prophylaxis for moderate emetogenic chemotherapy included intravenous 5-HT3 antagonists (Palonosetron administered as a single fixed 10 μg/kg dose (maximum total dose of 0.75 mg) infused over 30s or 50 μg/kg of Granisetron in a single dose administered over five minutes, and it was based on data available from previous pediatric studies.[15] Both drugs were delivered via IV route 30min before initiating moderately emetogenic. Patients with [?] 1-2 episodes of breakthrough vomiting received intravenous Dexamethasone [for body surface area (BSA) [?] 0.6m2; 2 mg twice a day and for BSA >0.6 m2; 4 mg twice a day] as a rescue.

The patient sample size was calculated using:

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`image1.emf` available at https://authorea.com/users/412061/articles/520878-does-a-single-dose-of-palonosetron-have-any-role-in-preventing-chemotherapy-induced-nausea-and-vomiting-in-pediatric-patients-a-double-blind-randomized-controlled-trial

Where N is the Population size and e is the level of precision. For the present study, the population's size was determined based on the previous number of patients admitted because of Osteosarcoma, N is 228 patients for one month, and e is 0.05 at 95% confidence Interval n = 200. The two groups received equal patients. Although a total number of 228 patients got enrolled in each arm, there was an approximately 12 % dropout for different reasons. Therefore, a total number of 200 patients were evaluated, i.e., 100 patients in each group.

Patients satisfying the eligibility criteria were randomized, regardless of age and sex, to receive either palonosetron or Granisetron using a computer-generated randomization schedule. The schedule was packed in a sealed envelope, which the two designated persons opened during the beginning of chemotherapy. All patients were randomly allocated to group I (palonosetron, n=100) and group II (Granisetron, n=100).

Except for the independent pharmacists dispensing the research drugs at the hospital and the study drug assigner, all study staff and participants were blinded to treatment assignment for the study duration. They were also forbidden from releasing any drug allocation data to other persons.

Outcome Variables:

The evaluation of Emesis was based on the following parameters: nausea (presence or absence) and vomiting (frequency, duration, and severity)

The MANE scale, i.e., Morrow Assessment of Nausea and Emesis[18] were used to appraise the parameters; however, this scale was modified in this study to apply to children. This scale was initially being used to evaluate adult emesis and consisted of a questionnaire consisting of the following events: anticipatory nausea and vomiting, nausea, dry heaving, and post-chemotherapy vomiting. It considers the quantification of these events' duration by adult patients based on the amount of time that nausea and vomiting continue to occur.

It is a method of evaluating symptoms on a six-point scale from the beginning of chemotherapy treatment to 24 hours later. To be applied to children, the MANE scale has to be updated, and outside variables that could affect the results of the research, such as children's parents and caregivers such as nurses or doctors, could also be part of it[14].

At 2, 4, 6, 8, 12, 18, and 24 hours after the start of chemotherapy treatment, the child was left to tell us whether nausea was present or absent. To homogenize the evaluation and adjust the MANE scale to pediatric patients, the authors made these modifications[14].

The following definitions were used in the evaluation: a) Nausea has been characterized in the upper gastrointestinal tract as a subjective sensation of repugnance. Usually, it was a prodromal symptom of vomiting. (b) Vomiting was a retrograde and vigorous removal of stomach contents.

Acute emesis was identified as any vomiting during the period starting with the first chemotherapy dose and continuing until 24 hours after the last chemotherapy dose was completed in that block (acute phase). A full response was described as the absence of acute vomiting without rescue medication (CR). If the patient had 1-2 episodes of vomiting without the use of rescue medication, the response was deemed partial and failure if the patient had more than 2 episodes and/or the use of rescue medicine. Rescue medication was given to the children who had more than 2 vomiting episodes[9,15].

For children who vomit after receiving dexamethasone, add-on, rescue medicines is allowed to give 0.025 mg/kg/dose of Lorazepam for chronic vomiting at the discretion of the treating primary care doctor.

A predesigned format was used for all details of the patient. A notebook was given to the patient or their guardians for easy documentation of the emetic episodes. For a given session of chemotherapy, the responsibility was given to the child or their parents to inform us regarding each and every incidence of vomiting for a period of 2, 4, 6, 8, 12, 18, and 24 hours from the completion of chemotherapy or last dose of rescue medicines.

The response was reported as episode number and timing (to distinguish full response/partial response/failure) and rescue medication use. The primary efficacy endpoint was CR patients' proportion during the acute period in the first on-study cycle. The secondary endpoint was the proportion of patients in the first on-study period needing rescue antiemetic treatment during the acute process. The response was also analyzed in the group I (Palonosetron) and group II (Granisetron) arms of all subsequent chemotherapy sessions during the study period.

To avoid the confounding effect of anticipatory vomiting, subjects were not included during subsequent courses of chemotherapy.

The adverse events related to the palonosetron or Granisetron were carefully evaluated by taking a relevant history and physical examination at the time of initiation of chemotherapy, on discharge, and during the next chemotherapy session. Lab investigations were done as per the chemotherapy session scheduled, including complete blood count, Liver function tests, and Renal Function Tests. All sorts of adverse events were recorded as per the CTCAE, i.e., Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 available at National Cancer Institute website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Adverse events were recorded for up to 10 days from the day of administration of the drug, and the treating physician's opinion on the relationship of the adverse events to the study drug was also recorded.

Statistical Analysis

The researchers have hypothesized that the palonosetron group is better than the granisetron group to achieve a complete response (CR) following moderate emetogenic therapy for Osteosarcoma. Alternatively, a null hypothesis was given by the researchers which advocates that there was not statistical difference exists among the two groups. The level of significance was adjusted to a p-value equal to 0.05. To test the null

hypothesis and compare the CR between the 2 groups, an independent t-test (continuous variables) and χ^2 test for categorical variables.

The statistical analysis was carried out using IBM SPSS software version 21. The univariate analysis was carried out to evaluate the risk factors associated with emesis, and the frequency distribution was done for the various demographic factors considered and other clinical parameters in the study. The relative risk was measured to evaluate the risk between the two groups administered Palonosetron and Granisetron. The chi-square test of association was done to evaluate the association of the response to antiemetic prophylaxis for the study groups. The statistical analysis was carried out at a 95% confidence level with the level of significance at 0.05, i.e., $p<0.05$.

RESULTS:

The study's sample size was 228 patients, and they were randomly allocated to group I, i.e., Palonosetron and Granisetron, i.e., group II. A total number of 28 patients were excluded from the study, and 200 were eligible for the assessment.

Essentially, the distribution of all variables in the two groups was balanced. These 200 patients obtained 604 blocks of chemotherapy.

Figure 1presents the flow diagram for patient recruitment and selection.

Among the 200 subjects equally distributed in the two groups and administered palonosetron and Granisetron, there were 68% males and 32% females in group I and 64% males and 36% females in group II. The mean age in group I was 10.2±2.8 years, and group II was 10.5±1.9. There were 37% patients less than 10 years and 63% were above 10 years of age in group I, while group II had 39% patients less than 10 years and 61% patients more than 10 years of age. The rescue dose of dexamethasone was given to 17% of patients in group I and 28% in group II (*Table 1).*

The complete response (CR) was seen in 83% of patients in group I, while 72% showed complete response (CR) in group II which was statistically significant, i.e., $p<0.05$. The relative risk was 0.65, i.e., the risk of vomiting was 0.65 times less in group I than group II, i.e., $p<0.05$, which was statistically significant (*Table 2).*

The relative risk of breakthrough vomiting was lesser in the Palonosetron arm across all chemotherapy cycles than the Granisetron arm, i.e., $p<0.05$, which was statistically significant (*Table 3).*

The rescue medicine, dexamethasone, was the only statistically significant predisposing factor as the $p<0.05$. The other factors like gender, age, and type of Osteosarcoma were not statistically significantly associated with emesis (*Table 4).*

Ten patients (2 in Palonosetron arm and 8 in the Granisetron arm) had headaches, and 6 patients (three in each arm) had constipation requiring laxatives in the first to-study chemotherapy cycle. Similarly, 14 patients had abdominal pain (8 in the Palonosetron group and 6 in the Granisetron group), and 10 patients had diarrhea (4 in the Palonosetron arm and 6 in the Granisetron arm). These were considered related to the drug by the treating physician. There were no serious adverse events associated with both drugs and none that required discontinuation owing to these events.

Discussion

The prime reason behind this cohort study was to compare single-dose palonosetron with Granisetron for CINV after the treatment of osteosarcoma in pediatric patients. The outcomes of this study suggest the confirmation of the alternate hypothesis, i.e., there was a significant difference among the groups for complete response and relative risk of breakthrough emesis ($p < .05$), because the group I demonstrated a substantial downside incidence of vomiting and decreased risk of breakthrough vomiting with group II.

The incidence of complete response in group I and group II were 83% and 72% ($p<0.05$), respectively, and the risk of breakthrough vomiting in group I was 0.65 lesser than group II ($p<0.05$) at 24 hours of follow-up.

Similarly, the alternate hypothesis was valid for a number of rescue medications, i.e., a significant difference exists among group I and group II ($p<0.05$).

Based on the end results, the use of palonosetron is warranted in the treatment of moderately emetogenic CINV in the treatment of osteosarcoma of pediatric patients is warranted and could be associated with a decreased risk of undesirable side effects, such as breakthrough vomiting in the post-operative period and inconvenience caused by it to the patients and parents.

The most annoying adverse effects of chemotherapy are nausea and vomiting, especially in pediatric patients with osteosarcoma having moderately emetogenic therapy.

Due to the multiple adverse effects of chemotherapeutic agents, a combination of antiemetic agents must be tested, such as stimulating the dopamine D2 receptor in the chemoreceptor trigger zone (CTZ) and binding of the neurokinin-1 (NK-1) receptor with substance P in the postrema area[9,19].

Although a corticosteroid's addition improves the potency of 5-HT3 receptor antagonists against CINV in different clinical trials, the best standard single-dose treatment of 5-HT3 receptor antagonists for pediatric emesis has not been demonstrated, particularly in the acute chemotherapy phase, i.e., the first 24 hours. Few studies have reported the potency of the dopamine D2 receptor antagonist for the prevention of acute emesis[9]; however, the guidelines for the prevention of CINV due to faults in the study's design do not consider these regimens.

Although a 5-HT3 receptor antagonist has been delivered multiple times to control acute CINV in past clinical trials, particularly randomized clinical trials, superiority to single-dose prechemotherapy administration has not been shown[10]. Contemporary literature indicates that a 5-HT3 receptor antagonist, steroid, and NK-1 receptor antagonist[10] are the most common practice for blocking nausea and vomiting initiated by strongly or moderately emetogenic chemotherapy[9].

Palonosetron interacts with the 5-HT3 receptor competitively while ondansetron and Granisetron exhibit strict competitive anti-competitive interactions. The dual activity of Palonosetron in the 5-HT3- receptor is believed to increase the inhibitory effect on the primary receptor because alosteric interactions can induce receptor conformation differences. The dual action of the Palonosetron on the 5-HT3-receptor is expected at the primary receptor bunding point to trigger an enhanced inhibitor effect[9].

CINV, whether it is delayed or acute, palonosetron was found to be safer and potent enough for the prevention of CINV in adults with fixed doses. However, there was no consensus on using palonosetron in fixed doses in pediatric patients receiving chemotherapy for various malignancies. Recently, POGO, ESMO, and MASCC guidelines were released on the inclusion of Palonosetron for pediatric patients receiving MEC and HEC[20,21].

In the present study, a complete response of 83% was seen in group I, whereas a complete response of 72% was seen in group II during the first on-study cycle of chemotherapy.

At all intervals except zero-two, the Palonosetron mean adjusted MANE scores were significantly lower ($p<0.001$*). The adjusted MANE scale makes these symptoms sensitive and easy to relate to pediatric patients, even when they are treated as outpatients. In a similar study, for the granisetron and metoclopramide plus dimenhydrinate classes, the proportion of all chemotherapy treatments provided to patients with a full response (not more than one episode of vomiting) was 80% and 27.5%, respectively ($p < 0.001$).

Moreover, the current study's finding was in accordance with the previous studies where the rate of CR of palonosetron was found to be between 60-94%,[15, 21-27]. This was attributed to the receptor binding proposition property of palonosetron. Furthermore, long-lasting effects on receptor-ligand binding and functional responses to serotonin can be associated with this sort of receptor interaction. Palonosetron was found to be effective and safe.

In certain studies, age, gender, type of tumor, emetogenicity of the regimen, and choice of prophylactic agents have been shown to influence the response rate[15, 18-22]. However, in the present study, factors like age, gender, treatment regimen, and the number of rescue medications were risk factors for predicting CR

during the overall phase. Moreover, it was found that Dexamethasone was the only statistically significant predisposing risk factor ($p<0.05$). The other factors like gender, age, type of osteosarcoma, and treatment regimen were not statistically significantly associated with emesis.

This study's major strength was that a fixed dose of palonosetron was used for pediatric patients who underwent MEC especially designed for osteosarcoma of children, and these dosages were based on BSA and bodyweight of the child. However, these parameters were in contrast with other researchers who advocated using a single fixed dose of palonosetron regardless of the BSA and bodyweight of the child[14-15]. Secondly, the modified MANE score was followed, specially designed for the pediatric group to evaluate the CINV more effectively. Thirdly, this study was performed exclusively for pediatric patients who underwent MEC according to the POGO guidelines for osteosarcoma.

This randomized clinical trial has several limitations. Firstly, this was a single-center study with a smaller sample size to establish palonosetron's superiority over granisetron. Large multicenter trials are needed to lead to a clinically meaningful difference. Secondly, the potency of the palonosetron needs to be investigated in other pediatric patients with other malignancies undergoing MEC or HEC chemotherapy so that CINV can be controlled more effectively and improve their quality of life. Thirdly, the present study was limited to the acute phase of the CINV, i.e., the first 24 hours, and it has not explored the response rate in the delayed phase of CINV.

Conclusion:

Palonosetron seems to be safe and potent in pediatric patients with osteosarcoma in preventing CINV in a fixed dose of 10μg/kg. It is quite a resourceful drug alone in controlling CINV with minimal requirement of rescue medications. Furthermore, it could be helpful in developing nations with limited resources.

Abbreviations: CNIV: Chemotherapy-induced nausea and vomiting; MEC: moderate emetogenic chemotherapy; HEC: High emetogenic chemotherapy.

Declarations:

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee of the Chengdu Jinniu District People's Hospital and Ya'an People's Hospital. And comply with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The written informed consent was taken from all the patients.

Consent to publish: Not Applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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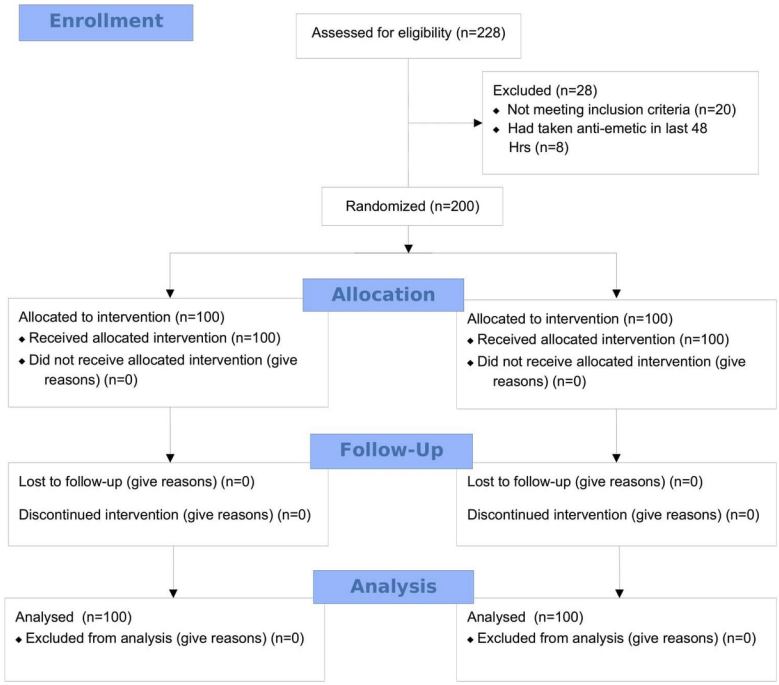
Figure Legend:

Figure 1: Illustrates the patient recruitment and selection.

Figure 1

Flow Diagram for Patient Recruitment and selection



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`Tables.pdf` available at https://authorea.com/users/412061/articles/520878-does-a-single-dose-of-palonosetron-have-any-role-in-preventing-chemotherapy-induced-nausea-and-vomiting-in-pediatric-patients-a-double-blind-randomized-controlled-trial