Does a single dose of palonosetron have any role in preventing acute chemotherapy-induced nausea and vomiting in pediatric osteosarcoma patients without dexamethasone? A randomized clinical trial

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Abstract

Background. Chemotherapy-induced nausea and vomiting (CINV) is a troublesome side-effect of chemotherapy in pediatric patients undergoing osteosarcoma treatment. In this context, the role of 5-hydroxytryptamine-3 (5-HT3) receptor antagonists needs to be explored.

Objectives. To evaluate the superiority of single-dose palonosetron over granisetron in pediatric patients undergoing highly emetogenic chemotherapy (HEC) for osteosarcoma.

Materials and methods. In this double-blind, randomized study, pediatric patients were assessed in terms of acute nausea and vomiting following HEC for osteosarcoma. These children were assigned to group 1 (palonosetron) and group 2 (granisetron) without any other antiemetic prophylaxis. The primary outcome variable was the children's segment with a complete response (CR) during the acute phase of the 1st on-study chemotherapy cycle. The risk factors associated with the emesis were analyzed. The patients were followed up for the first 24 h after chemotherapy.

Results. A total number of 200 children were evaluated in terms of the response, and other factors that might alter the response were assessed in the 2 groups. These 200 children underwent 604 blocks of chemotherapy. Complete responses were documented in 83% and 72% of children receiving palonosetron and granisetron, respectively, during the acute phase. Only dexamethasone, used as a rescue medication, was found to be a significant risk factor that predisposed to the response ($p < 0.05$).

Conclusions. Single-dose palonosetron is an effective alternative to granisetron for preventing CINV in children receiving HEC for osteosarcoma.

Key words: granisetron, chemotherapy, emesis, 5-HT3 receptor antagonists, palonosetron

Background

Cancer is tormenting and devastating, but with the incessant emergence of medical advances, chemotherapy is launched as one of the reassuring measures. The advent of chemotherapy combined with radiotherapy and surgery re-established 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 bothersome, especially for children, leading to a compromised quality of life after chemotherapy.[1,2]

According to the emetogenic classification of Pediatric Oncologic Group of Ontario (POGO) from October 2017, various drugs commonly used for the chemotherapy of osteosarcomas in children are classified as highly emetogenic (cisplatin intravenously (i.v.) ≥12 mg/m^2/dose; doxorubicin i.v. ≥30 mg/m^2/dose; and methotrexate i.v. ≥12 g/m^2/dose) and moderately emetogenic (methotrexate i.v. 5 g/m^2/dose; and doxorubicin i.v. 25 mg/m^2/dose).[3] Moreover, even with the best antiemetic regimes, nausea and vomiting continue to be the most irksome aftermath of chemotherapy in children.[3]

Cisplatin- or doxorubicin-induced emesis was predominant before the 1980s. In the 1990s, a combination of a corticosteroid and a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist became customary practice. The use of high-dose metoclopramide and dexamethasone proved to be effective to a certain degree.[4] However, specific adverse effects, especially extrapyramidal reactions, commonly found in children and adolescents, have curbed the use of high-dose metoclopramide.

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

The combination of dexamethasone with first-generation 5-HT3 receptor antagonists is effective against acute CINV[9–14]; however, a second-generation 5-HT3 receptor antagonist, palonosetron, which is dynamic, extremely selective, and has great receptor binding capacity along with prolonged plasma half-life (40 h), is quite potent as a single dose in preventing both acute and delayed CINV related to MEC and HEC.[9–13] Still, very few studies have been conducted so far to establish the superiority of single-dose palonosetron over the combination of drugs to control CINV in patients undergoing HEC.[9,14–16]

No standard pediatric antiemetic treatment has yet been implemented, considering all advances and the inclusion of newer and improved medication regimens in the treatment of CINV. This research was carried out on this unique population prone to nausea and vomiting in order to assess the effectiveness and side effects of antiemetics.

Objectives

The goal of this study was to evaluate the efficacy of palonosetron compared to granisetron in treating CINV in pediatric patients who received HEC for osteosarcoma. The research primarily focused on estimating the prevalence of CINV after applying the 2 drugs.

Materials and methods

Patient recruitment and selection

To fulfil the research objectives, the authors planned a randomized, controlled, double-blind clinical trial, which was conducted at the Department of Pediatrics of Chengdu University, China. The study was approved by the institutional review board and the local ethical committee (protocol CU # RC/IRB/2016/1042). All the procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional research committee of Chengdu Jinniu District People's Hospital and Ya'an People's Hospital in China, and comply with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all the participants.

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

All patients without systemic complications who strictly satisfied the inclusion criteria were included.

The exclusion criteria were as follows: children with abnormal liver function test (LFT) or renal function test (RFT) results, or those with organic disorders likely to cause vomiting; children who were on concurrent radiotherapy or received radiotherapy within 1 week prior to the study period; patients who were on antiemetic therapy within the first 24 h of recruitment; patients with known hypersensitivity toward any study drug; and patients with other adverse effects associated with chemotherapy. Furthermore, the anticipatory vomiting could create confusion in the results; the participants were not scheduled for successive chemotherapy.

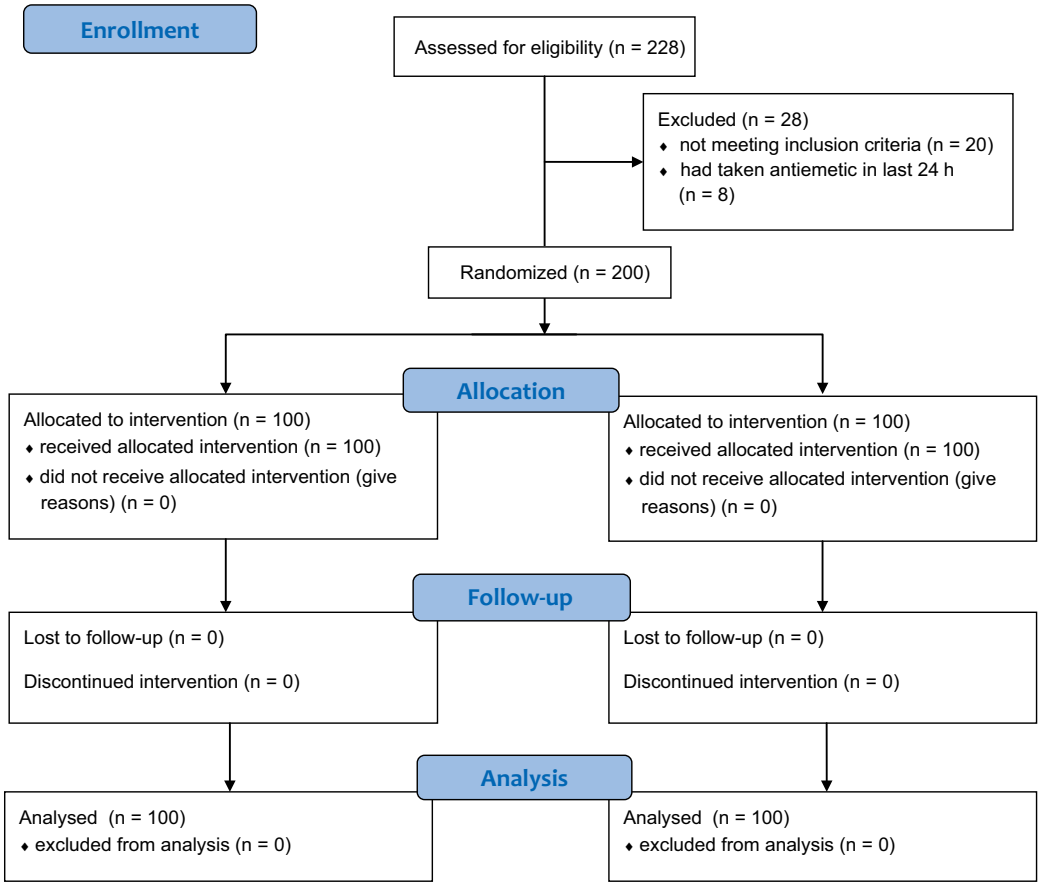

Fig. 1. Patient recruitment and selection (Consolidated Standards of Reporting Trials (CONSORT) flow diagram)

The patient sample size was calculated using the following formula (Equation 1)[17]:

$$n = \frac{N}{1 + N(e)^2} \quad (1)$$

where:
n – sample size;
N – population size; and
e – level of precision.

For the present study, the population size was determined based on the number of patients admitted to hospital or referred to treatment due to osteosarcoma (total population size: N = 228 for 1 month, and e is 0.05 at 95% confidence interval (95% CI)). The 2 groups received an equal number of patients. Although, a total of 228 patients were enrolled in the study. Approximately 12% of subjects, i.e., 28 subjects, did not meet the inclusion criteria. Therefore, a total number of 200 patients were evaluated, i.e., 100 patients in each group.

The osteosarcoma therapy regimen according to the EURAMOS-1 guidelines was used[14]:

– high-dose methotrexate (12 g/m^2) in 1 L of 5% dextrose water solution with 1 mEq/kg of sodium bicarbonate administered as a 4-hour infusion + etoposide (75 mg/m^2 i.v.) over 1 h in 250–500 mL saline serum and ifosfamide (3 g/m^2/day i.v.) over 3 h in 250–500 mL saline serum;

– cisplatin 120 mg/m^2 (a 4-hour infusion of 60 mg/m^2 per day), doxorubicin (70 mg/m^2) administered as a 6-hour continuous infusion, and high-dose methotrexate (12 g/m^2) in 1 L of 5% dextrose water solution with 1 mEq/kg of sodium bicarbonate, administered as a 4-hour infusion.

The POGO guidelines were followed for classifying the emetogenic potential of each chemotherapy regimen.[3] Single- or multiple-day chemotherapy was considered as 1 session.

Standard antiemetic prophylaxis for HEC included a 5-HT3 receptor antagonists, i.e., palonosetron administered i.v. in a single fixed dose of 20 μg/kg (maximum total dose of 0.75 mg) over 30 s, or granisetron administered i.v. in a single dose of 40 μg/kg over 5 min; it was based on the data available from previous pediatric studies.[15] Both drugs were delivered via the intravenous route 30 min before initiating HEC. Patients with 1–2 episodes of breakthrough vomiting received dexamethasone i.v. (for body surface area (BSA) ≤0.6 m^2, 2 mg twice a day, and for BSA > 0.6 m^2, 4 mg twice a day) as a rescue medication.

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 2 designated persons opened at the beginning of chemotherapy. All patients were randomly allocated to group 1 (palonosetron; n = 100) or group 2 (granisetron; n = 100).[17]

Except for the independent pharmacists dispensing the research drugs at the hospital and the person

responsible for drug allocation, all study staff and participants were blinded to treatment assignment for the study duration. They were also forbidden to reveal any drug allocation data to other persons.

Outcome variables

The evaluation of chemotherapy-induced nausea (CIN) or CINV was based on the following parameters: nausea (presence or absence); and vomiting (frequency, duration and severity).

Following the instructions, the patient or their caregiver kept track of emetic episodes and the degree of nausea in the diaries given. The children used the pediatric nausea assessment tool (PeNAT)[18] to self-report nausea intensity twice a day, in the morning and at bedtime at the very least, as well as any other time the child felt nauseous or their guardian thought the child would feel nauseous. The PeNAT is made up of 3 parts: determining the words or expressions for nausea that are used in each child's family; a script that focuses the child's attention on the subjective symptoms of nausea and explains the PeNAT; and a four-faced nausea severity scale. A co-investigator gave the PeNAT to each kid initially, and then taught the child's caregiver how to use it. The caregiver or a healthcare practitioner might help the patient complete nausea severity evaluation, but they could only record the information supplied by the child. They did not make the proxy evaluation of the child's nausea intensity. While monitoring the acute stages of CINV, the patients or their caregivers were approached in person to encourage adherence to research protocols and collect the completed diaries. The number of times the child vomited was subtracted from the number of vomiting episodes noted in the health record, if the child has not completed the diary in which they mentioned the number of vomiting episodes.

The following definitions were used in the evaluation: 'nausea' – the sensation of being about to vomit; usually, it was a prodromal symptom of vomiting; and 'vomiting' – a retrograde and vigorous removal of the stomach contents.

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

For children who vomit after receiving dexamethasone, an add-on rescue medicine is allowed – lorazepam at a dose of 0.025 mg/kg for chronic vomiting at the discretion of the treating primary care doctor.

A pre-designed worksheet was prepared for the patient so that all details could be included. To facilitate the documentation of emetic episodes, a notebook was provided to the patient or their caregiver. For a particular session of chemotherapy, the responsibility was given to the child or their parents to inform the researchers on each and every incidence of vomiting for a period of 2, 4, 6, 8, 12, 18, and 24 h from the completion of chemotherapy or the last dose of rescue medicines.

The response was reported as the number and timing of episodes (to distinguish CR/a partial response/failure) and the use of rescue medications. The primary efficacy endpoint was the proportion of CR patients during the acute period in the 1st on-study cycle of chemotherapy. The secondary endpoint was the proportion of patients in the 1st on-study cycle needing rescue antiemetic treatment during the acute period. The response was also analyzed in the group 1 (palonosetron) and group 2 (granisetron) arms of all subsequent chemotherapy sessions during the study period.

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

The adverse events related to palonosetron or granisetron were carefully evaluated by taking a relevant history and conducting a physical examination at the time of the 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 (CBC), LFT and RFT. All sorts of adverse events were recorded according to Common Terminology Criteria for Adverse Events (CTCAE), v. 4.03, available at the National Cancer Institute website (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40). Adverse events were recorded for up to 10 days from the day of the administration of the drug; the treating physician's opinion on the relationship between adverse events and the study drug was also recorded.

Statistical analyses

The researchers hypothesized that the palonosetron group would be better than the granisetron group in terms of CR following HEC for osteosarcoma. Alternatively, a null hypothesis was given by the researchers, which advocated that there was no statistically significant difference between the 2 groups. The level of significance was adjusted to a p-value equal to 0.05. To test the null hypothesis and compare CR between the 2 groups, the χ^2 test for categorical variables was conducted.

The statistical analysis was carried out using the IBM SPSS Statistics for Windows software, v. 21.0 (IBM Corp., Armonk, USA). 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 (RR) was measured to compare the RR of emesis between the 2 groups. The χ^2 test was used to evaluate the association between the response and antiemetic prophylaxis for the study groups. All data, except for age, were categorical in nature, involving only frequencies with mutually exclusive independent variables and the expected frequency count for each cell of the tables >5. In the light of these characteristics, the χ^2 test was chosen as the appropriate test for the study.

The statistical analysis was carried out at 95% CI, with the level of significance set at 0.05, i.e., $p < 0.05$ was considered as a statistically significant difference.

Results

The study sample size was 228 patients, randomly allocated to group 1 (palonosetron) and group 2 (granisetron). A total of 28 patients were excluded from the study, and thus 200 were included in the analysis. These 200 patients received 604 blocks of chemotherapy. Figure 1 presents the flow diagram for patient recruitment and selection.

Essentially, the distribution of all variables in the 2 groups was balanced.

Among the 200 subjects equally distributed in the 2 groups, there were 68% males and 32% females in group 1, and 64% males and 36% females in group 2. The mean age in group 1 was 10.2 ±2.8 years, and in group 2, it was 10.5 ±1.9 years. There were 37% patients aged ≤10 years and 63% aged >10 years in group 1, while group 2 had 31% patients aged ≤10 years and 69% aged >10 years (Table 1).

Table 2 shows the response to antiemetic prophylaxis doses in both study groups. A complete response was observed in 83% of patients in group 1, while in group 2, 72% of patients showed CR. A partial response was evident in 11% of the participants from group 1 and in 23% in group 2. The failure of antiemetic prophylaxis was evident in 6% in group 1, whereas in group 2, the percentage of failure was 5%. The difference in the response to antiemetic prophylaxis between the study groups was statistically significant ($p = 0.002$). The RR value for antiemetic prophylaxis was 0.65 (95% CI: [0.26; 2.81]), i.e., the risk of vomiting was 0.65 times smaller in group 1 than in group 2, with a p-value of 0.040, which was statistically significant (Table 2).

Table 3 presents the RR values in both study groups during the subsequent cycles of chemotherapy. The RR of breakthrough vomiting was lesser in the palonosetron arm across all chemotherapy cycles when compared to the granisetron arm (Table 3).

The univariate analysis results regarding factors that might affect the response to antiemetic prophylaxis in both groups are summarized in Table 4. Gender, age and the type of osteosarcoma did not significantly influence the response in either group ($p > 0.05$). The prophylactic dosage of a rescue medicine, dexamethasone, was the only statistically significant predisposing factor associated with emesis ($p = 0.001$), as shown in Table 4.

Ten patients (2 in group 1 and 8 in group 2) had headaches, and 6 patients (3 in each arm) had constipation requiring laxatives during the 1st on-study chemotherapy cycle. Similarly, 14 patients had abdominal pain (8 in group 1 and 6 in group 2) and 10 patients had diarrhea (4 in group 1 and 6 in group 2). These effects were considered by the treating physician as related to the drug. There were no serious adverse events associated with either drug, and none that required the discontinuation of the therapy.

Table 1. Baseline demographic and disease characteristics in the study groups

Characteristic		Group 1 n = 100	Group 2 n = 100
Gender n (%)	male	68 (68)	64 (64)
	female	32 (32)	36 (36)
Age [years] n (%)	M ±SD	10.2 ±2.8	10.5 ±1.9
	≤10	37 (37)	31 (31)
	>10	63 (63)	69 (69)
Type of osteosarcoma n (%)	peripheral	33 (33)	39 (39)
	medullary (axial)	67 (67)	61 (61)

Group 1 – palonosetron; Group 2 – granisetron; n – number; M – mean; SD – standard deviation.

Table 2. Response to antiemetic prophylaxis in the study groups (χ^2 test)

Response	Group 1 n = 100	Group 2 n = 100	χ^2	p-value	RR	95% CI	p-value
CR	83 (83)	72 (72)	34.812	0.002*	0.65	[0.26; 2.81]	0.004*
Partial response	11 (11)	23 (23)					
Failure	6 (6)	5 (5)					

Data are presented as n (%). CR – complete response; RR – relative risk; 95% CI – 95% confidence interval; * statistically significant.

Table 3. Relative risk (RR) of vomiting in the palonosetron arm in comparison with the granisetron arm during the subsequent cycles of chemotherapy

Cycle	RR	95% CI
1st cycle	0.78	[0.48; 1.89]
2nd cycle	0.61	[0.33; 2.23]
3rd cycle	0.81	[0.51; 2.95]
4th cycle	0.88	[0.62; 2.98]
5th cycle	0.72	[0.47; 3.19]
6th cycle	0.71	[0.39; 3.69]

95% CI – 95% confidence interval.

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 confirm the hypothesis stating that there would be a significant difference between the groups in terms of CR and RR of breakthrough emesis ($p < 0.05$); group 1 demonstrated a substantial downside incidence of vomiting and a decreased risk of breakthrough vomiting in comparison with group 2.

Based on the end results, the use of palonosetron is warranted in the prevention of CINV in osteosarcoma pediatric patients undergoing HEC, and could be associated with a decreased risk of undesirable side effects, such as breakthrough vomiting in the postoperative period and the resultant inconvenience for patients and their parents.

Due to the multiple adverse effects of chemotherapeutic agents, a combination of antiemetic agents must be tested, such as preventing the stimulation of dopamine D2 receptor in the chemoreceptor trigger zone (CTZ) and binding neurokinin-1 (NK-1) receptor with substance P in the area postrema.[19,20]

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

Although a 5-HT3 receptor antagonist has been administered multiple times to control acute CINV in previous clinical trials, particularly randomized clinical trials (RCTs), the superiority of single-dose pre-chemotherapy administration has not been shown.[10] The contemporary literature indicates that a combination of a 5-HT3 receptor antagonist, a steroid and a NK-1 receptor antagonist[10] is the most common practice for blocking nausea and vomiting initiated by MEC or HEC.[9]

Palonosetron interacts with the 5-HT3 receptor both competitively and non-competitively, while ondansetron and granisetron exhibit strictly competitive antagonistic properties. The dual activity of palonosetron against 5-HT3 receptor is believed to increase the inhibitory effect on the primary receptor, since allosteric interactions can induce receptor conformation changes.[9]

Palonosetron at fixed doses has been found to be safe and potent enough to prevent CINV, whether acute or delayed, in adults.[20] However, there is no consensus on using palonosetron at fixed doses in pediatric patients receiving chemotherapy for various malignancies. Recently, the POGO and Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guidelines have been released on the inclusion of palonosetron for pediatric patients receiving MEC and HEC.[21,22]

In the present study, at all intervals except zero-two, the palonosetron PeNAT mean adjusted scores were significantly lower ($p < 0.001$) than when compared to granisetron. It means that the children have reported less episodes of vomiting when compared to granisetron group. In a similar study, for the granisetron and metoclopramide+dimenhydrinate groups, the proportion

Table 4. Univariate analysis of factors that might affect the response to antiemetic prophylaxis

Potential risk factor for emesis		CR (both groups) n = 155	Partial response or failure		X^2	p-value
			group 1 n = 17	group 2 n = 28		
Gender	male	104 (67.1)	12 (70.6)	16 (57.1)	42.34	0.230
	female	51 (32.9)	5 (29.4)	12 (42.9)		
Age [years]	≤10	46 (29.7)	12 (70.6)	10 (35.7)	23.91	0.410
	>10	109 (70.3)	5 (29.4)	18 (64.3)		
Type of osteosarcoma	peripheral	54 (34.8)	8 (47.1)	10 (35.7)	18.19	0.310
	medullary (axial)	101 (65.2)	9 (52.9)	18 (64.3)		
Dexamethasone	yes	92 (59.4)	14 (82.4)	23 (82.1)	27.81	0.001*
	no	63 (40.6)	3 (17.6)	5 (17.9)		

CR – complete response. Data presented as n (%). * statistically significant.

of CR patients (not more than 1 episode of vomiting) was 80.0% and 27.5%, respectively ($p < 0.001$).[18]

Moreover, the findings of the current study are in accordance with previous research, where the rate of CR due to palonosetron was 60–94%.[15,22–30] This was attributed to the receptor binding potential 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 has proven to be effective and safe.

In certain studies, gender, age, the type of tumor, the emetogenicity of the regimen, and the choice of prophylactic agents have been shown to influence the rate of CR.[15,19–23] In the present study, factors like gender, age, the treatment regimen, and the number of rescue medications (dexamethasone) were evaluated as potential risk factors that might affect the response during the overall treatment. It was found that the use of dexamethasone was the only statistically significant predisposing risk factor. Other factors, like gender, age, the type of osteosarcoma, and the treatment regimen, were not statistically significantly associated with emesis.

The major strength of this study is that a fixed dose of palonosetron was used for pediatric osteosarcoma patients who underwent HEC, and the dosage was based on the child's BSA and body weight. In contrast, other researchers advocated using a single fixed dose of palonosetron regardless of the child's BSA and body weight.[14,15]. Secondly, the PeNAT scale was specially designed for the pediatric group to evaluate CINV more accurately. Thirdly, this study was performed exclusively on pediatric patients who underwent HEC, according to the POGO guidelines for osteosarcoma.

Limitations

This RCT has several limitations. Firstly, it was a single-center study with a smaller sample size to establish the superiority of palonosetron over granisetron. Large multicenter trials are needed to lead to clinically meaningful conclusions. Secondly, the potency of the palonosetron needs to be investigated in other pediatric patients with other malignancies, undergoing MEC or HEC, so that CINV can be controlled more effectively and the patients' quality of life can be improved. Thirdly, the present study was limited to the acute phase of CINV, i.e., the first 24 h, and it did not explore the rate of CR in the delayed phase of CINV. Moreover, the present study was not enrolled in the clinical trial registry for RCTs.

Conclusions

Palonosetron seems to be safe and potent when used in a fixed dose of 20 μg/kg in pediatric patients with osteosarcoma in preventing CINV. It is quite effective alone in controlling CINV with a minimal requirement for rescue medications. Furthermore, it could be recommended in developing countries with limited resources.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

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