Comparison of antiemetic efficacy and safety of palonosetron vs ondansetron in the prevention of chemotherapy-induced nausea and vomiting in children

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Background Chemotherapy-induced nausea and vomiting (CINV) in children is a major side effect despite the use of combination antiemetic drugs.
Objective To compare the efficacy and safety profile of palonosetron, a second-generation 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist, with ondansetron in the prevention of CINV in children.
Methods A prospective, randomized, crossover study was conducted in patients aged 2-18 years. 160 chemotherapy cycles, consisting of chemotherapy drugs with moderate- and high-emetogenic potential, were studied. The study group received a single dose of intravenous (IV) palonosetron 5 mcg/kg, and the standard group received IV ondansetron 5 mg/m^2 every 8 hours while receiving chemotherapy. The patients were observed for vomiting, use of rescue antiemetic medications, and nausea from Day 1 0-72 hours after completion of each chemotherapy cycle. All adverse events during the study period were recorded.
Results The overall percentage of patients with complete response (CR) in the palonosetron and ondansetron groups were 60% and 56.2%, respectively (P = .631). The CR rates in the palonosetron and ondansetron groups were 75% and 70%, respectively, in the acute phase (P = .479), and 68.8% and 65%, respectively, in the delayed phase (P = .614). There was no statistically significant difference in the CR rates cross both groups.
Conclusion A single dose of palonosetron is noninferior to ondansetron in the prevention of CINV in children and can be considered as an alternative antiemetic drug. There was no significant difference in adverse effects between the palonosetron and ondansetron group.

Chemotherapy-induced nausea and vomiting (CINV) continues to be a significant problem in children with cancer,[1] and the antiemetic treatment for the prevention of CINV remains a challenge. A 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist is one of the most commonly used antiemetic drugs for the prevention of CINV.[2] The safety and efficacy profiles of the first-generation 5-HT_3 receptor antagonists ondansetron, granisetron, and dolasetron have been shown to be equal when used at equipotent doses.[3] However, despite the use of various first-generation 5-HT_3 receptor antagonists as a prophylactic antiemetic treatment, CINV remains the main adverse event of chemotherapy and has a negative impact on patient quality of life.[4,5]

Palonosetron is a highly potent second-generation selective 5-HT_3 receptor antagonist that has a strong receptor-binding affinity and a prolonged plasma-elimination half-life (21-37 hours in pediatrics, and more than 41 hours in adults).[6-8] The safety and efficacy of palonosetron in the prevention of acute and delayed CINV has been established in adults.[9,10] Palonosetron was approved by the United States Food and Administration (FDA) in 2014, so there are few studies reporting on the safety and efficacy of palonosetron compared with the first-generation 5-HT_3 receptor antagonist.[8,11-13] We conducted a randomized crossover comparative study to evaluate the efficacy and safety of palonosetron compared with ondansetron in the prevention of CINV in children who receive either moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC).

Materials and methods

Study population

Chemotherapy-naive patients aged 2-18 years with

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either histologically or cytologically confirmed cancer were eligible for the study. They were scheduled to receive at least 2 consecutive identical cycles of chemotherapy consisting of either MEC or HEC drugs. Patients who developed vomiting as a result of organic causes (ie, syndrome of inappropriate antidiuretic hormone secretion [SIADH], gastrointestinal obstruction, electrolyte imbalance, and raised intracranial tension) during the study period were excluded. Patients who received antiemetic drugs within 24 hours of the proposed chemotherapy, those scheduled to receive radiotherapy on study days 1–5, and patients diagnosed with either a seizure disorder or any condition requiring anticonvulsants or sedatives during chemotherapy days were not included in the study. A written informed consent was obtained from patients and their parents before study entry.

Study design

The total number of chemotherapy cycles with the expected difference in efficacy of 20% between the standard and the study drug was 160. A chemotherapy cycle consisted of 1 day, 3 days, and 5 days of injections followed by a gap of 2 weeks after the last injection before starting the next cycle. Patients were randomized by computer-generated blocks to receive chemotherapy with either palonosetron for the first cycle followed by ondansetron for the next cycle, or ondansetron for the first cycle followed by palonosetron for the second cycle. Each pair of chemotherapy cycles was randomized. The standard antiemetic regimen included intravenous (IV) ondansetron 5 mg/m^2 30 minutes before chemotherapy and every 8 hours thereafter on all days of chemotherapy. The antiemetic regimen included a single dose of IV palonosetron 5 μg/kg 30 minutes before chemotherapy on Day 1. In addition, all patients across both groups on HEC drugs received a single dose of IV dexamethasone 10 mg/m^2 30 minutes before chemotherapy on all days of treatment. The chemotherapy drugs were classified as MEC and HEC according to the Pediatric Oncology Group of Ontario 2011 guidelines.[14] Patients who had 2 or more episodes of vomiting received either a combination of metoclopramide 0.15 mg/kg with promethazine 0.5 mg/kg IV over a 30-minute infusion or oral metoclopramide (0.15 mg/kg) with the dose repeated as needed. The number and timing of each vomiting episode and use of rescue antiemetic drug were recorded from the beginning of each chemotherapy cycle to 72 hours after completion of therapy. This study was approved by the ethical committee of our institute.

Efficacy parameters

Efficacy was monitored through clinical evaluations and based on patients' diary entries. From the start of chemotherapy (time 0 hr) until 72 hours (3 days) after the completion of chemotherapy, patients used their diaries to document the date and time of emetic episodes and their use of rescue medication, as well as twice daily nausea ratings on the Edmonton's Symptom Assessment Scale (ESAS). The ESAS measures the intensity of nausea felt by the patienton a scale of 0-10 (0 = least severe; 10 = most severe) and was recorded by either the patient or the caretaker.[15]

Safety

All adverse events (AEs) irrespective of whether the patient received the study or the standard drug were documented.

Statistical analysis

The statistical observations of the categorical variables were evaluated by using the chi-square and Fischer exact tests as appropriate and SPSS 16.0 windows software (IBM, Armank, NY). The primary endpoint was complete response (CR; defined as no emesis and no rescue medication) during the overall period (from initiation of chemotherapy to 72 hours after completion of chemotherapy). Secondary end points were: the evaluation of CR rates in the acute phase (initiation of chemotherapy to 24 hours after therapy) and the delayed phase (24 hours to 72 hours after therapy); overall-, acute-, and delayed-phase CR rates in chemotherapy cycles consisting of 1-, 3-, and 5-day therapy; and a comparison between the groups of the use of rescue antiemetics, nausea scores, and adverse events. The observed side effects were analyzed using the Fisher exact test. Statistical significance was defined as $P < .05$.

Results

Data from 170 chemotherapy cycles administered to 37 patients were included in the study. Five pairs of chemotherapy cycles (10 cycles) were excluded as follows: electrolyte imbalance (2 patients); gastrointestinal infection (1 patient); SIADH (1 patient); and increased intracranial tension (1 patient). Among the total 160 cycles studied, 122 cycles were of HEC drugs and 38 cycles were of MEC drugs. Most of the cycles consisted of 3 days of injections (72 cycles). The details of patient characteristics and chemotherapy are shown in Table 1. As a result of crossover stratification, the distribution of patients by gender, chemotherapeutic history, and corticosteroid use was similar among all treatment groups. The most common types of malignant disease treated were Hodgkin lymphoma (35%), germ cell tumor (12.5%), rhabdomyosarcoma (12.5%), neuroblastoma (10%), osteosarcoma (8.7%) retinoblastoma (7.5%), and others (10%). The most commonly used drugs used were adriamycin, dacarbazine, and cisplatin (Table 2).

The CR during the overall period was 60% in the palonosetron group, and 56.2% in ondansetron group ($P = .631$; Table 3). The percentage of patients with overall CR in palonosetron and ondansetron groups as per number of chemotherapy days were 51.7% and 44.8% in 1-day ther-

TABLE 1 Characteristics of patients and chemotherapy

Characteristic	Value
Patients	
Total no. of patients	37
Median age (range)	7 y 7 mo (2 y 2 mo-17 y)
Male, n	19
Female, n	16
Body-mass index, kg/m^2 (range)	15 (12.3-25.5)
Chemotherapy[a]	
Total no. of cycles[b]	160
MEC	38
HEC	122
1-day	58
3-day	72
5-day	30

HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

[a]Unit for all entries under this heading is "cycles." [b]A chemotherapy cycle consists of 1 day, 3 days, and 5 days of injections, followed by a break of 2 weeks after the last injection before starting the next cycle.

TABLE 2 Underlying malignancies and chemotherapies used

Underlying malignancy	
Malignancy, chemotherapy regimen	No. of patients, cycles
Hodgkin lymphoma, ABVD	13, 56
Germ cell tumor, PEB	5, 20
Neuroblastoma, OPEC	5, 16
Rhabdomyosarcoma, IE+VAC	4, 20
Osteosarcoma, adriamycin-cisplatin	3, 14
Peripheral neuroectodermal tumor, VAC	2, 10
Retinoblastoma, CEV	2, 12
Synovial sarcoma, Ifos-Adria	1, 6
Desmoplastic small round cell tumor, VAC+IE	1, 6
Chemotherapy	
Drug	No. of cycles
Adriamycin	86
Cisplatin	46
Carboplatin	22
Cyclophosphamide	30
Ifosfamide	36
Actinomycin D	2
Dacarbazine	66

ABVD, adriamycin, bleomycin, vinblastin, dacarbazine; CEV, carboplatin, etoposide, vincristine; IE, ifosfamide, etoposide; OPEC, vincristine, cisplatin, etoposide, cyclophosphamide; PEB, cisplatin, etoposide, bleomycin; VAC, vincristine actinomycin D, cyclophosphamide

apy, 55.6% and 50% in 3-day therapy, and 40% and 33.3% in 5-day therapy, respectively. The difference in overall CR rates across both the groups was not statistically significant. The number and percentage of patients with CR in the acute and delayed phases as per the duration of chemotherapy are presented in Table 4.

The percentage of patients with no nausea during the overall period across the 2 groups were similar (53.8% in the ondansetron group, and 48% in the palonosetron group; $P = .485$). The median severity of nausea on the ESAS scale (0–10) was always less than 4 (ie, no more than mild nausea) in both treatment groups.

The overall percentages of patients who received rescue antiemetic drugs in the palonosetron and ondansetron groups were 29.3% and 31.5%, respectively. The percentage of rescue antiemetic drugs used across both groups as per duration of chemotherapy is shown in the Figure.The percentages of all AEs across the groups were similar (Table 5). Most of the AEs were mild in severity and not related to the study medication. The most common AEs for both groups were constipation and headache.

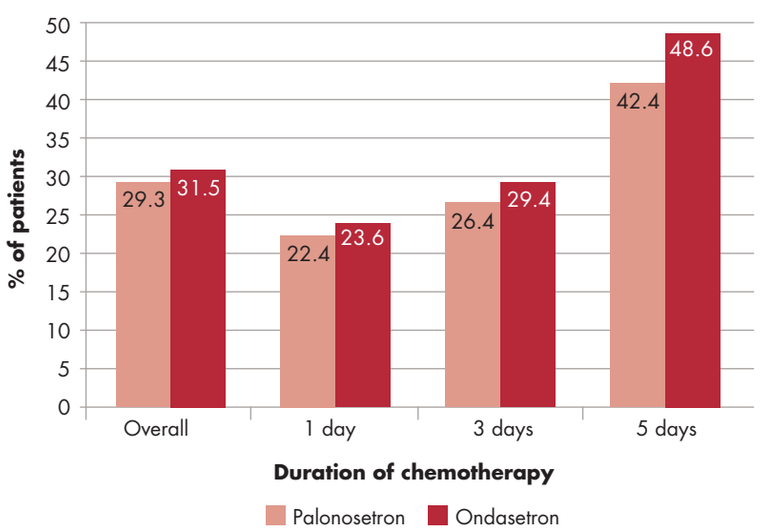

FIGURE Percentage of patients receiving rescue antiemetics as per chemotherapy schedules in the palonosetron and ondansetron groups.

TABLE 3 Complete response rate by chemotherapy schedule

Chemotherapy schedule (no. of cycles)	No. of patients with CR (%)		*P* value
	Palonosetron	Ondansetron	
Overall (160)	48 (60)	45 (56.2)	.631
1-day (58)	18 (62.1)	17 (58.6)	.788
3-days (72)	23 (63.9)	21 (58.3)	.629
5-days (30)	7 (46.7)	6 (40)	.713

TABLE 4 Complete response rates in acute and delayed phases by chemotherapy schedule

Schedule (no. of cycles)	Complete response rate		*P* value
	Palonosetron, n (%)	Ondansetron, n (%)	
Total (160)			
Acute	60 (75)	56 (70)	.479
Delayed	55 (68.8)	52 (65)	.614
1 day (58)			
Acute	23 (79.3)	22 (75.9)	.753
Delayed	21 (72.4)	18 (62.1)	.401
3 days (72)			
Acute	27 (75)	25 (69.4)	.599
Delayed	25 (69.4)	24 (66.7)	.800
5 days (30)			
Acute	10 (66.7)	9 (60)	.705
Delayed	9 (60)	8 (53.3)	.713

TABLE 5 Adverse effects of palonosetron and ondansetron

Adverse effect	Palonosetron, n (%) (n = 80)	Ondansetron, n (%) (n = 80)
Headache	7 (8.7)	5 (5.7)
Dizziness	0 (0)	1 (0.8)
Constipation	7 (8.7)	11 (13.7)

Discussion

Palonosetron has been recommended as an effective alternative drug to first-generation 5-HT_3 receptor antagonists for use in the prevention of both acute and delayed CINV in the adult population receiving both MEC and HEC.[16] Very few studies have evaluated the efficacy of palonosetron in the prevention of CINV in children.[8,11-13]

A major strength of the current study is that all patients received a dose of palonosetron based on their weight, and a crossover comparison of the same patients receiving conventional ondansetron was studied. This was not the case in the studies by Kadota and colleagues[8] and Sepúlveda-Vildósol and colleagues,[11] in which all of the patients received the same dose of palonosetron regardless of their weight. In the studies by Ripaldi and colleagues[12] and Nadaraja and colleagues,[13] all of the patients received a weight-related dose but were not compared with the conventional antiemetic.

Although the study done by Sepúlveda-Vildósol and colleagues[11] showed that efficacy of palonosetron compared with ondansetron in preventing CINV was statistically significant for the initial 3 days (percentages of CR in palonosetron and ondansetron for days 1, 2, and 3 were 92% vs 72%, 72% vs 46%, and 78% vs 54%, respectively) that was not the case in our study. The reason may be that in our study, dexamethasone was given in both the palonosetron and ondansetron groups for all children who received HEC. The addition of dexamethasone as an antiemetic might explain the comparable CR rates across both groups in our study.

The study by Nadaraja and collegaues[13] using palonosetron 5μg/kg in children having a 24-hour infusion of high-dose methotrexate chemotherapy showed CR rates of 84% and 60% in the acute and delayed phases, respectively. The CR rate in the acute phase was comparable but it was lower in delayed phase compared with the results of our study (CR rates in acute and delayed phases of 1-day chemotherapy; 79.3% and 72.4%, respectively).

Palonosetron was recently approved in the United States for the prevention of CINV in children (aged 1 month to 17 years).[17] The Helsinn group showed that a dose of 20 μg/kg of palonosetron is noninferior to ondansetron (0.15 mg/kg every 4 hours/day for a maximum of 32 mg/day) with an acute CR rate of 59.4% in the palonosetron group compared with 58.6% in the ondansetron group. The current study has a similar CR rate of 60% but with the use of a much lower dose of palonosetron.

Neurokinin receptor-1 (NK-1) antagonists comprise a new group of antiemetic drugs recommended for the prevention of CINV in adults.[16] Gore and colleagues have shown that the combination of the NK-1 receptor antagonist, aprepitant, with ondansetron and dexamethasone resulted in a CR rate of 60.7% in the acute phase and 35.7% in the delayed phase in children aged 12 years and older.[18] The recent guidelines by the Pediatric Oncology Group of Ontario have recommended the use of aprepitant in combination with a 5-HT_3 receptor antagonist and dexamethasone in children above aged 12 years.[2]

The percentage of patients who required rescue antiemetic

drugs in this study was not statistically significant between the 2 groups. There was a high need of rescue antiemetics in the 5-day chemotherapy schedule, especially in the delayed phase, compared with the 1-day and 3-day schedule. The half-life of palonosetron is less than 40 hours, which might explain the high failure rates in the 5-day schedule.

The most important clinical advantage of palonosetron over the first-generation 5-HT_3 receptor antagonists is its prolonged half-life resulting in fewer doses per chemotherapy cycle. So far, ondansetron and granisetron are the preferred drugs in the prevention of CINV in children who receive chemotherapy.[2,14] We found that 1 dose of palonosetron will suffice for 66-72 hours of the initial postchemotherapy period for most patients.

The use of palonosetron as a standard prophylaxis for the prevention of CINV in pediatric patients who receive MEC and HEC would result in fewer administrations of IV injections compared with the first-generation 5-HT_3 receptor antagonists with comparable efficacy. This in turn would lead to a decreased work load for health care workers and a reduced risk of catheter-related infections because of the reduced frequency of injections. This is particularly important in underserved countries such as India, where there are limited resources for caring for children with cancer. In addition, patients are less willing to complete the treatment when they have suffered from the distressing side effects of chemotherapy. Although we did not examine the cost benefit between the 2 groups, the cost of 1 dose of palonosetron was equal to 4 doses of ondansetron (based on hospital pharmacy prices).

The main limitations of our study were that there was a low number of patients, and concomitant administration of other drugs such as antibiotics, antifungals, and antivirals, which may contribute to vomiting, were not taken into consideration.

In conclusion, our study shows that palonosetron is noninferior to conventional ondansetron in controlling acute and delayed CINV induced by MEC and HEC in pediatric patients. The drug palonosetron can be considered as an alternative 5-HT_3 receptor antagonist for the prevention of CINV in children. A CR rate of 60% when using available combinations of antiemetic drugs for CINV prevention in children is low, given that the target is 100%,and there is a need to study newer antiemetics in children.

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