Original Article

Comparison of oral aprepitant and intravenous fosaprepitant for prevention of chemotherapy-induced nausea and vomiting in pediatric oncology patients: a randomized phase III trial

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Background: Neurokinin-1 receptor antagonists have improved the management of chemotherapy-induced nausea and vomiting (CINV), but to date there has been no prospective comparison between oral aprepitant and intravenous fosaprepitant in pediatric oncology patients.

Methods: Our study was a double-parallel study, and the distribution ratio was 1:1. Children aged 2–12 years who were undergoing moderate or highly emetogenic chemotherapy (MEC or HEC) were randomly assigned to receive ondansetron and dexamethasone combined with either a single dose of intravenous fosaprepitant (arm A), or 3 days of oral aprepitant (arm B). The primary outcome measure was the rate of complete response (CR) of CINV within the acute phase, defined as from the start through 24 hours after the last chemotherapy dose. Response during the delayed phase, overall response, and use of rescue antiemetics were also assessed.

Results: We prospectively evaluated 108 eligible patients, including 55 receiving fosaprepitant. Study observations were made during a single cycle for each patient. The occurrence of CR in the acute phase was statistically higher for patients receiving fosaprepitant (95% *vs.* 79%, P=0.018<0.05). Modest differences were seen in CR rates during the delayed phase (71% *vs.* 66%, P=0.586), and overall response rate (69% *vs.* 57%, P=0.179). The use of antiemetic rescue medicines was similar between arms A (11%) and B (7%).

Conclusions: Fosaprepitant produced more CRs of CINV in the acute phase than did aprepitant, although there were no statistical differences in delayed phase response, overall response, or use of rescue antiemetics. This study confirms the safety, efficacy, and potential advantages of fosaprepitant in reducing CINV in pediatric oncology patients.

Trial Registration: ClinicalTrials.gov identifier: NCT04873284.

Keywords: Aprepitant; fosaprepitant; chemotherapy-induced nausea and vomiting (CINV); pediatric; antiemesis

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Introduction

Cancer patients frequently experience chemotherapy-induced nausea and vomiting (CINV) (1-3). These symptoms can result in poor nutrition and weight loss, increased infections, electrolyte disturbances, and worse quality of life in children undergoing cancer therapy (4). CINV most commonly occurs during or within 24 hours of completing chemotherapy (acute phase), but may also linger on or develop several days after finishing the regimen (delayed phase). Risks of CINV are clearly associated with particular chemotherapy agents, allowing for the categorization of regimens based on their expected likelihood of causing nausea and/or vomiting. For patients treated with moderate or highly emetogenic chemotherapy (MEC or HEC), recommendations and guidelines have been established for standard premedication with antiemetics (1-8). These recommendations include routine use of dexamethasone and 5-hydroxytryptamine 3 (5-HT3) antagonists such as ondansetron. More recently, the use of neurokinin-1 receptor antagonists has been recommended based upon the benefits of further reduction of CINV in adult and pediatric cancer patients (7,8). The two most commonly used drugs in this class of agents are oral aprepitant given daily for 3 days (9), and intravenous fosaprepitant given as a single dose. Fosaprepitant is a water-soluble prodrug that is converted by endogenous phosphatases into aprepitant following administration. To date, there has been no prospective controlled trial to help determine which of these agents may be superior in controlling CINV. We now report a randomized study of the use of dexamethasone, ondansetron, and either oral aprepitant or intravenous fosaprepitant in pediatric patients ages 2–12 years who are receiving either MEC or HEC regimens. We present this article in accordance with the CONSORT reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-598/rc).

Highlight box

Key findings

- In the acute phase, the addition of fosaprepitant to ondansetron and dexamethasone is more beneficial than the addition of aprepitant. Fosaprepitant and aprepitant are not substantially different from one another during the delayed and overall phases of prevention.

What is known and what is new?

- Neurokinin-1 receptor antagonists were recently recommended for prevention of chemotherapy-induced nausea and vomiting (CINV) in children aged 6 months and older.
- Fosaprepitant in combination with ondansetron and dexamethasone is more effective than aprepitant in preventing CINV in minors receiving moderate or highly emetogenic chemotherapy (MEC or HEC) during the acute phase.

What is the implication, and what should change now?

- Addition of fosaprepitant to ondansetron and dexamethasone is more effective than aprepitant for the prevention of CINV in pediatric patients treated with MEC or HEC during the acute phase.

Methods

This prospective randomized phase III study was conducted in the Department of Hematology/Oncology of the Shanghai Children's Medical Center, Shanghai, China. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and with the approval of the Institutional Review Board of Shanghai Children's Medical Center Affiliated with Shanghai Jiao Tong University School of Medicine (No. SCMCIRB-K2020120-2).

Patient selection

Eligible patients included children between the ages of 2 and 12 years who were diagnosed with malignancy and scheduled to receive MEC or HEC, using guidelines from the National Comprehensive Cancer Network (NCCN) which classified the risk of chemotherapy agents based on the incidence of nausea and vomiting without the use of antiemetics (10). Drugs characterized as MEC had a CINV risk of >30% to 90%, while agents listed as HEC had a risk of >90%. Patients ≥10 years were also required to have a Karnofsky score of at least 60, while a Lansky play performance score of at least 60 was required for patients younger than 10 years of age. Parents or their legal guardians were required to provide written informed consent, and the life expectancy of patients was at least 3 months.

The exclusion criteria were as follows: known history of QT prolongation or allergic reaction to any of the study drugs; receipt of radiation therapy to the abdomen or pelvis in the week prior to treatment; active infection or any uncontrolled concurrent illness other than cancer; and symptomatic primary or metastatic central nervous system cancer causing nausea and vomiting.

Eligible patients were enrolled after obtaining written informed consent from their legal guardians. Computer-generated random numbers were used to assign patients

Table 1 Proportion of patients achieving efficacy endpoints

Vomiting	Fosaprepitant (n=55)	Aprepitant (n=53)	*Z* value	P value
Acute			5.60	0.018*
Nil (CR)	52 [95]	42 [79]		
Mild	2 [4]	6 [11]		
Moderate	1 [2]	2 [4]		
Severe	0 [0]	3 [6]		
Delayed			0.297	0.586
Nil (CR)	39 [71]	35 [66]		
Mild	5 [9]	7 [13]		
Moderate	5 [9]	4 [8]		
Severe	6 [11]	6 [11]		
Overall			1.805	0.179
Nil (CR)	38 [69]	30 [57]		
Mild	6 [11]	10 [19]		
Moderate	4 [7]	5 [9]		
Severe	7 [13]	8 [15]		

Data are presented as n [%]. Grade of vomiting was defined as follows: grade 0 (nil): no vomiting (CR); grade 1 (mild): 1–2 episodes in 24 hours; grade 2 (moderate): 3–5 episodes in 24 hours; grade 3 (severe): ≥6 episodes in 24 hours, tube feeding, total parenteral nutrition, or hospitalization; grade 4 vomiting (life-threatening consequences, urgent intervention indicated); or grade 5 vomiting (death). *, P<0.05. CR, complete response.

meeting all inclusion criteria to one of two groups. At randomization, no consideration was given to nausea risk (MEC *vs.* HEC) or specific chemotherapy regimen. Shanghai Children's Medical Center Hematology/Oncology conducted the randomization. A diary of nausea and vomiting for up to 5 days after completing chemotherapy was completed by the parent/guardian accompanying the child and reviewed by the investigators.

Study treatment

The drug administration regimen was designed according to the antiemetic guidelines of the NCCN (10) and related studies (11). Patients on arm A received fosaprepitant (Chia Tai Tianqing Pharmaceutical, Nanjing, China) as a single infusion of 4 mg/kg (maximum 150 mg) 1 hour before chemotherapy on day 1 (12). Patients on arm B received oral aprepitant (Merck Sharp & Dohme Australia Pty Ltd., Lowe, NJ, USA) 1 hour before chemotherapy, 3 mg/kg on day 1 and 2 mg/kg on days 2 and 3. The dosage of aprepitant was determined based on data from a phase 1 study by Kang *et al.* (13). Aprepitant was given as a homogeneous suspension dissolved in water at a concentration of 25 mg/mL. The desired dose, calculated based on bodyweight, was drawn into a syringe and given orally. Patients on both arms received intravenous dexamethasone 0.225 mg/kg 30 minutes before chemo and for 2 days after aprepitant/fosaprepitant administration, and 0.45 mg/kg/day until 2 days after the last dose of chemotherapy. Due to the weak inhibition of the CYP3A4 enzyme in the liver by fosaprepitant, the dexamethasone dose was decreased by 50% for the first 48 hours after fosaprepitant administration, as determined by pharmacokinetic data from adult studies (13-16). Patients also received intravenous ondansetron 10 mg/m^2 daily until 2 days after the last chemotherapy. If the patient was discharged, these medications were given orally. Administration of additional rescue antiemetics was allowed except for additional doses of fosaprepitant or aprepitant, and use of these additional agents was recorded.

Response criteria

The acute phase was defined as any episode of vomiting/retching that occurred between the administration of the first dose of chemotherapy and 24 hours after the last dose of chemotherapy in the block. For example, monitoring for the acute phase for the single-day and 3-day protocols was continued until days 2 and 4, respectively. The delayed phase was defined as vomiting/retching occurring between 24 hours and 5 days after the final administration of chemotherapy. Assessment of the overall phase included both the acute and delayed phases. The occurrence of vomiting was documented by the caregiver diary and reviewed by the investigator. Also included in the vomiting diary were questions about chemotherapy-related toxicities, dietary habits, and rescue medication needs. A prospective record of vomiting or retching episodes was kept until 6 days after the last chemotherapy treatment. An explanation of vomiting episodes is provided in the footnote to *Table 1*.

Each patient was only studied for a single cycle of chemotherapy. Complete response (CR) was defined as the absence of vomiting, retching, or use of rescue medication. The primary endpoint of the study was the percentage of patients with CR during the acute phase of a single studied chemotherapy cycle. Secondary endpoints included the

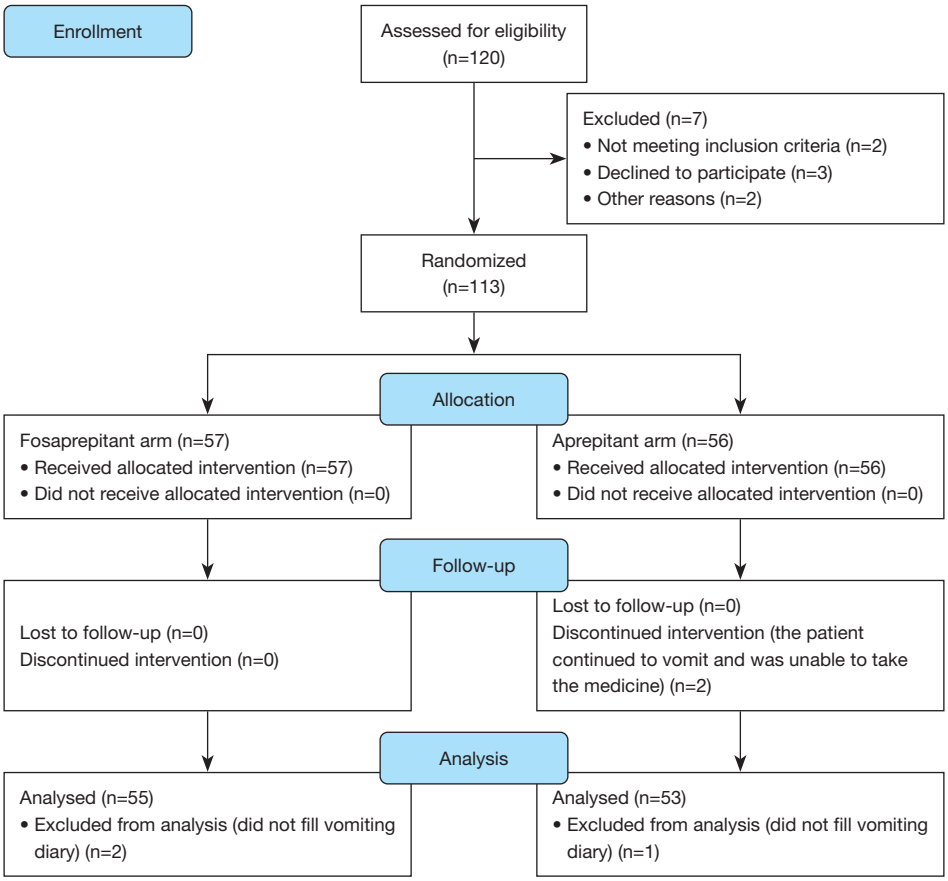

Figure 1 Flow chart of participant inclusion.

proportion of patients who achieved CR within the delayed phase, as well as CR for the overall chemotherapy cycle. In addition, adverse events (AEs) were collected as well for that chemotherapy cycle. AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (17). Patients were censored 3 weeks after the delayed phase was completed or until the next chemotherapy cycle began. The AEs of the patients were recorded until censoring occurred, after which the patients' case records and nursing records were reviewed to verify and record additional information.

Statistical analysis

Based on the available literature, we predicted that the CR rates to CINV in the acute phase would be 66% in the aprepitant group and 86% in the fosaprepitant group (11,13,18). To demonstrate the superiority of fosaprepitant over aprepitant with a power of 90% and a two-sided significance level of 5%, a sample size of 120 (60 in each arm) was required. In the investigation, patients were assigned randomly for only one chemotherapy cycle. Using descriptive statistics, all demographic and clinical details of the patients were examined. Categorical variables were compared using the chi-square test. The significance level (P value) for all two-sided analyses was set at 0.05. All statistical analyses were conducted with the software 22.0 (IBM Corp., Armonk, NY, USA). *T*-test was used for continuous variables.

Results

Patients

Between 1 December 2020 and 30 January 2021, 120 patients were screened for trial eligibility; 113 of these patients were enrolled and randomly assigned. *Figure 1* depicts the exclusionary criteria. We excluded one patient

Table 2 Baseline characteristics of treated patients

Characteristics	Fosaprepitant (n=55)	Aprepitant (n=53)	Z/χ^2	P value
Age (years)	8 (4–10.83)	7.83 (5.75–11)	Z=0.866	0.388
Gender				
Male	38	35	χ^2=0.115	0.735
Female	17	18		
Weight (kg)	26.2 (16.45–43.7)	27.8 (16.95–35.1)	Z=0.308	0.759
Prior exposure to chemotherapy	45 [82]	39 [74]	χ^2=1.059	0.304
Prior exposure to aprepitant/fosaprepitant	15 [27]	14 [26]	χ^2=0.01	0.92
Diagnosis				
Germ cell tumor	14 [25]	13 [25]	χ^2=0.012	0.912
Neuroblastoma	12 [22]	14 [26]	χ^2=0.312	0.576
Hepatoblastoma	12 [22]	7 [13]	χ^2=1.38	0.24
Medulloblastoma	9 [16]	7 [13]	χ^2=0.213	0.644
Rhabdomyosarcoma	3 [5]	4 [8]	χ^2=0.195	0.659
Primitive ectodermal tumor	4 [7]	1 [2]	χ^2=1.773	0.183
Undifferentiated sarcoma	1 [2]	4 [8]	χ^2=2.006	0.157
Osteosarcoma	0 [0]	2 [4]	χ^2=2.115	0.146
Adrenocortical carcinoma	0 [0]	1 [2]	χ^2=1.047	0.306
NCCN emetogenicity scale			χ^2=0.173	0.678
Moderate	3 [5]	2 [4]		
High	52 [95]	51 [96]		

Data are presented as M (P_{25}–P_{75}), n, or n [%]. NCCN, National Comprehensive Cancer Network; M, median; P, percentile.

in the aprepitant arm and two patients in the fosaprepitant arm due to incomplete vomiting diaries. Two additional patients in the aprepitant group were unable to consume the medication and continued to vomit, so they were excluded from the final analysis. In total, 108 people (53 in the aprepitant arm and 55 in the fosaprepitant arm) were evaluated (*Figure 1*). The average age was 7.96 (4.83–10.98) years. There were 35 girls (32%) and 73 boys (68%) enrolled in the study. The most common diagnosis was germ cell tumor (25% of patients), followed by neuroblastoma (24%). Using the NCCN scale, the great majority of patients were classified as receiving HEC (95% in the fosaprepitant arm and 96% in the aprepitant arm). Totals of 15 out of 55 (27%) patients in the fosaprepitant arm and 14 out of 53 (26%) patients in the aprepitant arm reported prior exposure to aprepitant or fosaprepitant. Before enrollment, the majority of patients (82% in the fosaprepitant arm and 74% in the aprepitant arm) were receiving treatment and had undergone chemotherapy. Comparable baseline characteristics existed between the two treatment groups. Regarding diagnosis, treatment, and emetogenicity of regimens, the proportion of patients in each arm was comparable (*Table 2*).

Prevention of CINV

A CR was attained in the acute phase in 52 (95%) of 55 patients in the fosaprepitant arm and in 42 of 53 (79%) in the aprepitant arm (P=0.018) (*Table 1*). The delayed phase CR rates for the fosaprepitant arm and the aprepitant arm were 71% *vs.* 66% (P=0.586), and the overall phase CR rates were 69% *vs.* 57% (P=0.179), respectively (*Table 1*). Rescue anti-emetics were used by 4 patients (7%) in the fosaprepitant arm and 6 patients (11%) in the aprepitant

Table 3 AEs reported among participants

AEs	Fosaprepitant (n=55)	Aprepitant (n=53)	χ^2	P value
Headache	1 [2]	5 [9]	2.984	0.084
Fever	2 [4]	1 [2]	0.306	0.580
Anorexia	10 [18]	10 [19]	0.008	0.927
Abdominal discomfort	5 [9]	7 [13]	0.463	0.496
Cough	0 [0]	1 [2]	–	0.491†
Diarrhea	2 [4]	1 [2]	–	>0.99†
Constipation	9 [16]	13 [25]	1.109	0.292
Febrile neutropenia (grade 1–2)	7 [13]	10 [19]	0.767	0.381
Febrile neutropenia (grade 3–4)	6 [11]	5 [9]	0.604	0.800
Leukopenia (grade 1–2)	17 [31]	15 [28]	0.088	0.767
Leukopenia (grade 3–4)	4 [7]	7 [13]	1.039	0.308
Mucositis	2 [4]	0 [0]	–	0.496†
Thrombocytopenia (all grades)	2 [4]	1 [2]	–	>0.99†
Hematuria	1 [2]	0 [0]	–	>0.99†
Debilitation	8 [15]	9 [17]	0.121	0.728
Serious AEs	0 [0]	0 [0]	–	–

Data are presented as n [%]. †, Fisher's exact test. AE, adverse event.

arm (P=0.47). Seven patients in the fosaprepitant arm and 8 in the aprepitant arm developed grade 3 (severe) vomiting. Regardless of prior exposure to fosaprepitant or chemotherapy, patients in the fosaprepitant arm had significantly higher acute phase CR rates than those in the aprepitant arm overall.

Toxicity

The incidence of AEs in the two groups was comparable. Leukopenia grade 1–2 (31% *vs.* 28% in the two arms) and constipation (16% *vs.* 25%) were the two AEs that were most frequently reported (*Table 3*). Other side effects included nausea, vomiting, diarrhea, mucositis, thrombocytopenia, hematuria, debilitation, anorexia, headaches, febrile neutropenia, and leukopenia grade 3–4. All of these effects have been reported with chemotherapy administration. It is important to highlight that none of the individuals receiving fosaprepitant experienced thrombophlebitis as a result of the infusion, and no severe AEs were attributed to fosaprepitant or aprepitant.

Discussion

In adults, a single intravenous dose of 150 mg fosaprepitant on day 1 of cisplatin chemotherapy was comparable to a 3-day oral aprepitant regimen for the prevention of CINV in the 120 hours following chemotherapy (19). In pediatric patients receiving medications with at least a moderate risk of emesis, the acute and delayed CR rates for fosaprepitant were 86% and 79%, respectively (11). In contrast, CR rates in the acute and delayed phases in children receiving the 3-day oral aprepitant regimen were 66% and 51%, respectively (13). In a retrospective comparison, significantly more patients in the fosaprepitant group (35.6% of cycles) experienced complete control (no emetic episode, no use of rescue medication, and no emetic symptom more severe than mild nausea) than in the aprepitant group (12.5% of chemotherapy cycles, P=0.005) (20). To our knowledge, our study offers the first prospective comparison of these two agents. In our series, fosaprepitant was superior to aprepitant in preventing acute vomiting. The reasons for this are unclear, but perhaps are related to the faster and

more reliable achievement of meaningful drug levels, and/or the reliability of parenteral administration.

One potential advantage of fosaprepitant is the assurance that medication administration was successful, as two children in our study were omitted from the aprepitant group because they were unable to take an oral medication due to vomiting. For patients discharged after overnight chemotherapy administration, compliance with home dosing of oral aprepitant may be challenging, particularly in a nauseated child. In terms of cost-effectiveness, recent reports suggest an advantage for the use of single-dose fosaprepitant compared to the 3-day oral aprepitant regimen (21,22). Although hypersensitivity reactions and phlebitis have been reported in adults receiving fosaprepitant (23), these symptoms were not identified on this study in which fosaprepitant was infused through a central access device in all patients. There were no new safety indications of concern discovered. It is unknown whether antiemetic regimens based on NK1 have long-term toxicities or effects on growth and sexual maturation in minors. Even though the current data do not raise any particular concerns, longer-term monitoring of pediatric patients on aprepitant-based antiemetic regimens is essential.

Our study is limited by the absence of patients over the age of 12 years. The incidence of CINV increases with age throughout the pediatric spectrum (3), and the adolescent and young adult population was not included in this study. In addition, alternate drug schedules for pediatric patients have been approved by the US Food and Drug Administration for children. For example, patients may receive a single dose of fosaprepitant for injection on day 1 as done on this study, or fosaprepitant for injection on day 1 combined with aprepitant capsules or oral suspension on days 2 and 3 (12). That latter scheduling option was not studied in our trial, but could be considered in patients whose CINV requires an even more aggressive antiemetic regimen.

Conclusions

In conclusion, fosaprepitant in combination with ondansetron and dexamethasone was more effective in our study than aprepitant in preventing acute CINV in pediatric oncology patients receiving MEC or HEC. More comparable results were seen between the two agents in regard to control of delayed emesis, overall CINV, and use of rescue antiemetics. Fosaprepitant administration is convenient, safe, reliable, and potentially cost-effective, and can improve management of a significant problem in the treatment of young children with cancer.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-598/rc

Trial Protocol: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-598/tp

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-598/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-598/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-598/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and with the approval of the Institutional Review Board of Shanghai Children's Medical Center Affiliated with Shanghai Jiao Tong University School of Medicine (No. SCMCIRB-K2020120-2). Eligible patients were enrolled after obtaining written informed consent from their legal guardians.

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