Comparative study of fosaprepitant and aprepitant for the prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients

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Abbreviations	
NK-1	neurokinin-1
CINV	chemotherapy induced nausea and vomiting
CR	complete response
ASCO	American Society of Clinical Oncology
HEC	highly emetogenic chemotherapy

MEC	moderately emetogenic chemotherapy
RCT	randomized controlled trial
SCMC	Shanghai Children's Medical Center
CNS	Central Nervous System
IV	intravenous
CTCAE	Common Terminology Criteria for Adverse Events
FDA	Food and Drug Administration

Abstract

Background: Neurokinin-1 receptor antagonists was recently recommended for prevention of CINV in children aged 6 months and older. However there are limited data about how to choose NK-1 receptor antagonists, such as aprepitant and fosaprepitant in paediatric patients.

Procedure: Children aged 2-12 years scheduled to receive moderately or highly emetogenic chemotherapy were randomly assigned to arm-A (fosaprepitant) or arm-B (aprepitant). Children recruited to arm-A received intravenous ondansetron plus dexamethasone followed by fosaprepitant infusion. Children recruited to arm-B received the same drugs as those given to children in arm-A, except that fosaprepitant was substituted with aprepitant. Ondansetron and dexamethasone were given continuously until 48 hours after completion of chemotherapy. The primary end point of the study was to determine the proportion of patients who achieved a CR, defined as no vomiting, no retching, and no use of rescue medication, the proportion of patients who achieved a CR during the acute phase (0-24 hours) after administration of the last dose of chemotherapy. Secondary end points were the proportion of patients who achieved a CR during the 24-120 hours (delayed phase) and overall after administration of the last dose of chemotherapy.

Results: One hundred and eight patients were analyzed (55 in the fosaprepitant arm and 53 in the aprepitant arm). CR rates were higher in the fosaprepitant arm compared with the aprepitant arm during the acute phase (95 % vs 79 %, P =0.01< 0.05), delayed phase (71 % vs 66 %, P =0.89), and overall phase (69 % vs 57 %, P =0.18). Furthermore, the demand of rescue anti-emetics observed in fosaprepitant arm (7 %) has no difference with aprepitant arm (11 %). **Conclusion**: Addition of fosaprepitant to ondansetron and dexamethasone is more effective than aprepitant for the prevention of CINV in paediatric patients treated with moderately or highly emetogenic chemotherapy during the acute phase. However, there is no significant difference between fosaprepitant and aprepitant for prevention during the delayed and overall phase.

KEYWORDS: fosaprepitant, aprepitant, pediatric cancer, vomiting, efficacy, safety

1 INTRODUCTION

CINV, one of the most distressing side effects of chemotherapy[1], is a non-negligible side effect of cancer treatment, it affects up to 60% of patients receiving prophylactic anti-emetics[2,3]. Vomiting can lead to decreased body mass and resistance, increase the chance of infection and ultimately affect the next course of chemotherapy. The incidence and severity of CINV depend on a variety of factors[4], young age is a known risk factor for CINV, up to 70% of children experience vomiting symptoms.[5] Effective preventive regimens have been developed for adults, and there is also recommendation on children's antiemesis. According to ASCO Clinical Practice Guideline, children ≥6 months old receiving HEC should be treated

with high-emetic-risk antineoplastic agents like a three-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant.[6] The Pediatric Oncology Group of Ontario recommended that children older than 6 months receiving HEC which is not known or suspected to interact with aprepitant can be given granisetron or ondansetron or palonosetron + dexamethasone + aprepitant.[7] However, there are few data about how to choose NK-1 receptor antagonists, such as aprepitant and fosaprepitant in paediatric patients.

NK-1 receptor antagonists have potent and usually long-lasting anti-emetic activity against a broad spectrum of central and peripheral emetic agents, whereas 5-HT3 antagonists have a more restricted spectrum of activity with efficacy mostly against peripheral emetogens[8-10]. Prophylactic anti-emetic treatment with a NK-1 receptor antagonist in combination with a 5HT3 antagonist and/or dexamethasone is reported to show a high frequency of CINV control in children compared with 5-HT3 antagonist alone or 5-HT3 antagonist and dexamethasone combination[7]. Aprepitant, a potent, selective, oral NK-1 receptor antagonist, have shown to be clinically effective in preventing nausea and vomiting associated with emetogenic cancer chemotherapy[11-13]. Aprepitant in combination with a 5-HT3 antagonist and a corticosteroid, is indicated for the prevention of acute and delayed chemotherapy-induced nausea and vomiting due to moderately or highly emetogenic chemotherapy in adults[14]. Aprepitant capsule (adult formulation) is approved for children above 12 years of age. However, aprepitant oral suspension, used for children who could not

take capsules, is not available in many countries, which makes most pediatric patients only receive a 5-HT3 antagonist and/or dexamethasone as prophylactic anti-emetics. The instability of the commercially available oral aprepitant suspension with a short expiry of 72 hours after reconstitution also limits its application. In jurisdictions where aprepitant oral suspension is not available, it can only be prepared from capsules which makes it hard to prepare[15].

Fosaprepitant is another NK-1 antagonist and a prodrug of aprepitant, it is activated in the blood after intravenous administration. Fosaprepitant in combination with 5HT3 antagonist and dexamethasone which is recommended in adults for the prevention of CINV due to MEC or HEC is demonstrated to be efficacious[6,16]. The advantages of a single intravenous dose of fosaprepitant surpass a 3-day oral aprepitant schedule for preventing CINV in children including better compliance and more broad usage because it can be given intravenously in children who are unable to swallow oral capsules or are vomiting prior to the administration of chemotherapy. Furthermore, fosaprepitant is absorbed faster as an injection than an oral aprepitant, which makes it work faster. At the time of the initiation of our trial, there were few prospective data on the safety and efficacy of fosaprepitant for preventing CINV in children. The recently published guidelines for CINV in children emphasize the need of research on fosaprepitant use in children[14]. Although clinical studies on the safety and efficacy of aprepitant and fosaprepitant for antiemetic chemotherapy in children is available, there are still gaps in direct clinical studies comparing the efficacy and safety of these two drugs. In the present study, we, therefore, conducted a phase III

RCT to assess the safety and efficacy between fosaprepitant and aprepitant in combination with ondansetron and dexamethasone for prevention of CINV in pediatric patients.

2 METHODS

2.1 Study design and patients

The study was a phase III, randomized, superiority design, conducted in the department of Hematology/Oncology of SCMC, Shanghai, China. The study was approved by the Institute Ethics Committee and registered prospectively with Chinese Clinical Trial Registry (reference number: ChiCTR 2000040681). Patients were recruited after obtaining informed written consent from the parents. The primary objective of the study was to assess the efficacy between intravenous fosaprepitant and oral aprepitant for the prevention of CINV in pediatric patients receiving MEC or HEC, and the secondary objective was to assess the safety of fosaprepitant and aprepitant. NCCN clinical practice guidelines in oncology ranks single chemotherapeutic agents as low risk (<10%), mild risk (10-30%), moderate risk (30-60%), high risk (60-90%), and very high risk (>90%), on the basis of the frequency of causing nausea and vomiting without antiemetic treatment [17,18].

The major inclusion criteria were children aged 2-12 years at the time of study entry with documented cancer; scheduled to receive MEC or HEC (more than 30% emetogenic potential); with Karnofsky score of 60 or more (for patients aged greater than 10 years) or Lansky play performance score of 60 or more (for patients aged 10

years or less); predicted life expectancy of at least 3 months; and written informed consent provided by parent or guardian.

Major exclusion criteria were: vomiting 24 hours before treatment day 1; known history of QT prolongation or allergic reaction to any of the study drugs; symptomatic primary or metastatic CNS malignancy causing nausea or vomiting; patients who received radiation therapy to the abdomen or pelvis in the week before treatment; active infection or any uncontrolled concurrent illness except for malignancy; abnormal laboratory values at screening (peripheral absolute neutrophil count <1000 cells per μL, platelet count <100 000 cells per μL; alanine amino transferase or aspartate aminotransferase >5 times of the upper limit of normal for age, bilirubin or serum creatinine >1.5 times of the upper limit of normal for age); initiation of systemic corticosteroids within 72 hours before study drug administration or as part of the chemotherapy regimen; benzodiazepines or opioids initiated within 48 hours before treatment, except for single doses of triazolam, temazepam, or midazolam; use of antiemetics within 48 hours of treatment; use of CYP3A4 substrates or inhibitors within 7 days or CYP3A4 inducers within 30 days of treatment.

2.2 Randomization

Patients who met all the inclusion criteria were randomized to two arms using a computer-generated table of random numbers. The patients were not stratified during randomization according to the emetogenicity risk or chemotherapy duration. The randomization was performed by the department of Hematology/Oncology of SCMC. The clinical pharmacist preparing the drugs for administration and the investigator

writing the prescription were not blinded. The investigator collecting the data in the vomiting diary .

2.3 Procedures

Patients randomized to the aprepitant arm was given aprepitant (Merck Sharp & Dohme Australia Pty Ltd)30 min before initiation of chemotherapy on day 1, and in the morning on days 2 and 3. The dosage of aprepitant was determined based on the guideline written by Patel P et al [7]. For patients receiving chemotherapy on day 2 or 3, aprepitant was given 30 min before chemotherapy. Based on the study we selected 3.0 mg/kg on day 1 followed by 2.0 mg/kg on days 2 and 3 for further study in paediatric patients aged 2 years to less than 12 years. 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 randomized to the fosaprepitant arm received fosaprepitant (Chia Tai Tianqing Pharmaceutical, China) 4 mg/kg (maximum 150 mg) as a short IV infusion in normal saline (1 mg/ml) over 30 minutes.

Fosaprepitant and aprepitant were administered after ondansetron and dexamethasone had been given and 30 minutes prior to administration of chemotherapy.

The dosing and schedule of ondansetron and dexamethasone in both arms have been given in Table 1. The dexamethasone dose was reduced by 50% for the first 48 hours after administration of fosaprepitant based on pharmacokinetic data from adult studies that showed dexamethasone levels increased by 50% during the first 48 hours

after administration of fosaprepitant due to the weak inhibition of the CYP3A4 enzyme in the liver by fosaprepitant[19-21]. Rescue medications (except additional aprepitant) were permitted for vomiting as an add-on to ondansetron and dexamethasone therapy. The rescue agents included additional oral or intravenous ondansetron and/or dexamethasone, metoclopramide, domperidone, or olanzapine.

2.4 Definitions

Acute phase was defined as any episode of vomiting occurring after the administration of the first chemotherapy dose until 24 hours after the last chemotherapy dose in the block. Delayed phase was defined as vomiting occurring from 24 hours to 5 days after administration of the last dose of chemotherapy. For single-day and 3-day protocols, acute vomiting was evaluated up to day 2 and day 4, respectively. Overall phase included both acute and delayed phase assessment. Retching was included in the definition of vomiting.

2.5 Assessments

All the events were prospectively recorded in the vomiting diary by the parent/guardian. The diary was checked daily by the blinded investigator for patients admitted in the hospital, the entries by the parent/guardian were confirmed telephonically by the blinded investigator daily for patients discharged from the hospital. The vomiting diary contained questions regarding vomiting or retching along with some additional variables such as chemotherapy-related toxicities, food and fluid intake, and requirement of any rescue medication. The date and time of each vomiting or retching episode were recorded prospectively until 6 days after the last

chemotherapy. The grading of vomiting episodes has been provided as a footnote to Table 3. Adverse events recorded in the diary, were classified as per National Cancer Institute CTCAE version 4.0 by the investigator.[22] Patients were censored in the study 3 weeks after the completion of the delayed phase or till the beginning of the next cycle of chemotherapy, whichever was earlier. Adverse events were recorded until the patients were censored. The patients' case records, nursing, and medication charts were reviewed after censoring in the study to validate and record additional data.

2.6 Outcome

CR was defined as no vomiting, no retching, and no use of rescue medication. The primary end point was CR rates in the acute phase, and the secondary endpoints were CR rates in the delayed and overall phases.

2.7 Statistical analysis

Based on the available literature, we assumed that the CR rates to CINV in the acuted phase in the aprepitant group would be 60% and this would be 90% in the fosaprepitant group[23,24]. Allow for 10% loss, a sample size of 120 (60 in each arm) was required to show a superiority of fosaprepitant over the aprepitant with a power of 90% and a two-sided significance level of 5%. The patients were randomized in the study only once. Descriptive statistics were used to analyze the demographic and clinical characteristics of all the patients. Comparison between categorical variables was done by a chi-square test. All tests were two sided, and a significance level (P-value) of 0.05 was used. All the statistical analyses were carried out by SPSS statistical software (SPSS Inc., Version 22).

3 RESULTS

Between December 1, 2020 and January 30, 2021, 120 patients were screened for eligibility in the trial, of which 113 were enrolled and randomized. The reasons for exclusion are shown in Figure 1. One patient in aprepitant arm and two patients in fosaprepitant arm were excluded because they didn't fill vomiting diary. Two patients in the aprepitant arm continued vomiting and were unable to take the medicine, hence was excluded from the final analysis. Therefore, a total of 108 patients (55 in the fosaprepitant arm and 53 in the aprepitant arm) were analyzed. The median age was 17.5 years. The study included 73 (68%) males and 35 (32%) females. Nongerminomas germ cell tumor was the most common diagnosis, observed in 25% of patients, followed by 24% of Neuroblastoma. We had a larger proportion of patients in the high-risk group using the NCCN scale (95% in the fosaprepitant arm and 96% in the aprepitant arm). 15 of 55 (27%) patients in the fosaprepitant arm and 14 of 53 (26%) patients in the aprepitant arm had prior exposure to aprepitant or fosaprepitant. Most patients were undergoing treatment and had received chemotherapy prior to enrollment (82% in the fosaprepitant arm and 74% in the aprepitant arm). The baseline characteristics of patients were comparable between the two arms. Patients in both arms were balanced regarding diagnosis, chemotherapy, and the emetogenicity of regimens (Table 2).

3.1 Assessment of vomiting

52 of 55 patients (95%) in the fosaprepitant arm and 42 of 53 (79%) in the aprepitant arm achieved a CR in the acute phase ($P < 0.05$) (Table 3). The CR rates for

the fosaprepitant arm and the aprepitant arm were 71 % versus 66 % (P =0.89), during the delayed phase, and 69% versus 57% (P =0.18) , for the overall phase (Table 3). Four patients (7%) in the fosaprepitant arm and six patients (11%) in the aprepitant arm required rescue anti-emetics (P=0.47) (Figure2). Seven patients in the fosaprepitant arm and eight in the aprepitant arm developed severe vomiting. Overall, patients in the fosaprepitant arm had significantly higher CR rates in acute phase compared to those in the aprepitant arm, irrespective of previous exposure to fosaprepitant/aprepitant or chemotherapy.

3.2 Toxicities

Adverse events of the two groups were similar. Adverse events reported most in the study were Leukopenia-Grade 1-2 (31% vs 28% in the two arms) and constipation (9% vs 13 %) (Table 4). Other adverse events were abdominal discomfort, anorexia, headache, febrile neutropenia, leukopenia-Grade 3-4, fever, cough, diarrhea, mucositis thrombocytopenia, hematuria, debilitation. Of note, none of the patients receiving fosaprepitant developed thrombophlebitis due to the infusion. There was no serious adverse event in this study. No patient in the study developed CTCAE defined Grade 4 vomiting (life-threatening consequences; urgent intervention indicated) or Grade 5 vomiting (death) (Table 3).

4 DISCUSSION

It is reported that a 3-day oral aprepitant regimen in combination with ondansetron with dexamethasone, provided significant benefit in terms of prevention of nausea and vomiting associated with emetogenic chemotherapy in children and adolescents,

compared with a control regimen of ondansetron with or without dexamethasone. Irrespective of dexamethasone use, the proportion of patients who achieved a complete response with the aprepitant regimen than with the control regimen was higher across all phases[20]. Fosaprepitant is a prodrug of aprepitant and is administered intravenously. Fosaprepitant and aprepitant have been proven to be safe and efficacious for preventing CINV induced by MEC or HEC in adults in combination with an 5HT3 antagonist and dexamethasone[6,16-17,25]. However, there have been no published randomized trials comparing the efficacy and safety of fosappitant and aprepitant in children.

The dosage of aprepitant given in this study were modeled from phase 1 data for children aged 2 to 12 years. Based on initial simulations, body weight-based dose of 3 mg/kg on day 1 with 2 mg/kg on days 2 and 3 appeared to approximate the pharmacokinetic exposures seen in adults.[21]

The FDA of USA granted approval in April 2018 for the use of fosaprepitant in children above the age of 6 months[26]. For single-day MEC or HEC regimes, the FDA recommends a fosaprepitant dose of 4 mg/kg (age 2 to12 years) capped at 150 mg and infused over 1 hour. Of fosaprepitant, rolapitant, and netupitant are administered intravenously among the currently available NK-1receptor antagonists, however, only i.v. fosaprepitant is approved for use in pediatric patients[23-24,27-28]. An i.v. antiemetic is particularly attractive as a treatment option for CINV for some patients who might be unable to tolerate oral dosing[17,29-30].

Based on the study by Bakhshi et al[5], dexamethasone was used at 0.15 mg/kg/dose three times a day or a total dose 0.45 mg/kg/day, which is approximately equivalent to 13.5 mg/m^2/day. Because the adult data showed that fosaprepitant increased serum dexamethasone levels due to hepatic enzyme inhibition[31] we reduced the dexamethasone dose by 50% in the fosaprepitant arm for the first 48 hours.The recommended dose of ondansetron in children is 0.15 mg/kg (5 mg/m^2/dose) administered orally or intravenously q 8 hourly[32] and we use the same dose.

As reported, CR rates for fosaprepitant in pediatric subjects receiving drugs with at least a moderate risk of emesis were 81.1% and 47.3% in the acute and delayed phases, respectively. These CR rates are similar to those reported in the acute and delayed phases in children receiving the three-day oral aprepitant regimen (66% acute phase, 51% delayed phase) [22]. However, these studies were unable to compare whether there was a statistically significant difference in the prevention of vomiting between fosaprepitant and aprepitant. Our study found that fosaprepitant was superior to aprepitant in preventing acute vomiting. It may be because the intravenous fosaprepitant is absorbed faster and has higher utilization than the oral aprepitant. In our study, 2 children were excluded from the aprepitant group because they were unable to take oral medication due to vomiting, which again reminds us the indispensability of intravenous administration for some patients who might be unable to tolerate oral dosing. Kang et al reported significant improvement in CR with aprepitant in the acute phase (66% vs 52%, $P = 0.013$), the delayed phase (51% vs 26%, $P < 0.0001$), and over all phases (40% vs 20%, $P = 0.0002$).[22] The CR rates with

fosaprepitant in another trial for acute, delayed, and overall phases were 86%, 79%, and 70%, respectively[27]. These rates are higher than those reported with aprepitant. However, our study found that fosaprepitant is superior to aprepitant only in preventing acute vomiting. There is no significant difference in the prevention of delayed and overall phases.

Adverse events and serious adverse events were similar between groups and consistent with those in patients undergoing chemotherapy, and no new safety signals of concern were noted, compared with studies in adults. It is unknown whether there are any potential long-term toxicities of NK-1 based antiemetic regimens in children or long-term effects on growth and sexual maturation. Although the present data do not raise any specific concerns, longer term follow-up of paediatric patients treated with aprepitant-based antiemetic regimens is needed. According to the instructions, the most common adverse event of fosaprepitant is phlebitis. Enrolled patients received the administration of fosaprepitant via a central venous line and we did not observe any infusion-site reactions，which was reported an incidence of phlebitis of 2% in adult.[18]

The limitations of the study were that patients who use multi-day chemotherapy regimens only receive a single-day of fosaprepitant for injection on Day 1. However, FDA recommend children receive (6 months to 17 years) a single-day of fosaprepitant for injection on Day 1 (for single dose chemotherapy regimens) or fosaprepitant for injection on Day 1 and aprepitant capsules or oral suspension on Days 2 and 3 (for

single or multi-day chemotherapy regimens). But this did not affect the assessment of the effect of either drug on acute vomiting. Nonetheless, this is the first study comprehensively showing the efficacy and safety between fosaprepitant and aprepitant in children.

To conclude, fosaprepitant combined with ondansetron and dexamethasone is more effective than aprepitant during the acute phase for the prevention of CINV in children being treated with MEC or HEC.

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