CLINICAL INVESTIGATION

Aprepitant and Fosaprepitant Use in Children and Adolescents at an Academic Medical Center

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OBJECTIVE: To describe the use of aprepitant and fosaprepitant, a neurokinin 1 (NK-1) receptor inhibitor, in children and adolescents at a large academic medical center, for the prevention and management of chemotherapy-induced nausea and vomiting (CINV).

METHODS: A retrospective chart review was conducted using an electronic medical record system to evaluate the use of aprepitant and fosaprepitant in all pediatric patients that were discharged from a single academic medical center between February 25, 2009 and May 25, 2012.

RESULTS: Twenty-six patients were included in this review and received a total of 287 doses over the span of 114 cycles. Mean age was 10.1 years, with a range of 11 months to 17 years old. In 16 of 26 patients, aprepitant was used as the primary prophylaxis. Of those patients who received primary prophylaxis, 6 of 16 received it for highly emetogenic chemotherapy, and 10 of 16 received it for moderately emetogenic chemotherapy. Intravenous fosaprepitant was used in 7 of 26 patients, ages 13 to 17 (median 14) years old. No adverse effects attributable to aprepitant were reported.

CONCLUSIONS: Use of aprepitant and fosaprepitant in pediatric patients appeared to be well tolerated. No currently published reports data using aprepitant in a patient younger than 32 months old, whereas we reported its use in patients as young as 11 months old.

INDEX TERMS: antiemetics, aprepitant, nausea, vomiting

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INTRODUCTION

Generally, cancer treatment and management of the toxicities associated with treatment have drastically improved over the past several decades. Nevertheless, one of the most recognized and equally feared adverse effects of chemotherapy is nausea and vomiting. A survey of patients receiving chemotherapy noted that nausea and vomiting are the two side effects that are perceived as most distressing.¹ Nausea and vomiting have a significant impact on patients' quality of life, treatment compliance, and nutritional status. The introduction of newer antiemetics, including the neurokinin 1 (NK-1) receptor antagonist aprepitant has been a major advancement in the control of chemotherapy-induced nausea and vomiting (CINV).

Aprepitant (Emend; Merck & Co., Whitehouse

Station, NJ) was introduced in 2003 as an orally administered agent for acute and delayed CINV, and as an intravenously (IV) injected agent (fosaprepitant) in 2008. Aprepitant is approved for use in combination with a 5HT₃ receptor antagonist and a corticosteroid drug in moderate or highly emetogenic chemotherapy regimens.^{2,3} Aprepitant targets substance P and NK-1 receptors in the central nervous system, which has been shown to be effective at preventing CINV in adults in several large randomized trials.^{4,5} Aprepitant is included in guideline recommendations for management of CINV in adults⁶; however, no recommendations exist for the use of NK-1 inhibitors in the pediatric population, and very little evidence exists to guide safe and effective dosages for children younger than 11 years of age.

The recommended oral dosage for adults is 125 mg on day 1 followed by 80 mg on days 2 and

3. The initial approved adult dose was 115 mg IV 30 minutes prior to chemotherapy on day 1, followed by 80 mg of aprepitant orally on days 2 and 3. However, the 115-mg dose was discontinued in December 30, 2010, and the US Food and Drug Administration approved a single-dose fosaprepitant regimen (150 mg on day 1 with no aprepitant on day 2 or 3).^{2,7}

A randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of aprepitant for CINV was conducted in adolescents 11 to 19 years of age. Patients were randomized to a regimen of dexamethasone and ondansetron alone or in combination with oral aprepitant, 125 mg on day 1, followed by 80 mg daily for 2 days. Forty-six patients were enrolled, and aprepitant was well tolerated. Although response rates did not reach statistical significance, pharmacokinetic data suggested that adult dosages would be appropriate in this age group.⁸ This study is frequently used to justify aprepitant use and dosage in the adolescent population.

A retrospective chart review at a single institution evaluated aprepitant use in 32 pediatric patients. Data were reported from 146 total cycles of chemotherapy (70% received highly emetogenic chemotherapy [HEC], and 30% received moderately emetogenic therapy [MEC]).⁹ Patients' ages ranged from 32 months to 18 years, and their weight ranged from 13.6 to 65 kg. Patients weighing >20 kg received the adult dose of 125 mg on day 1, followed by 80 mg on days 2 and 3. Seven patients, all weighing <20 kg, received doses of 80 mg for 3 days. One patient, who weighed <15kg, received 80 mg on day 1 followed by 40 mg on days 2 and 3. The Children's Oncology Group (COG) does not restrict antiemetic use to any particular regimen.

West Virginia University Children's Hospital is a floor within an adult hospital and consists of 4 separate units: a 39-bed level 3 newborn intensive care unit, a 19-bed pediatric intensive care unit, a 28-bed general pediatric unit, and a 29-bed maternal infant care center. Children >11 years old receive the adult dose of aprepitant; children <11 years old are given 74 mg/m² on day 1 and 47 mg/m² on days 2 and 3. These doses are based on a clinical trial sponsored by Merck that is currently recruiting patients.⁹ Although we are not part of this trial, we incorporated aprepitant into our antiemetic regimen due to the excellent outcomes seen in our adult oncology population.

MATERIALS AND METHODS

This was a retrospective chart review conducted using the electronic medical record system to evaluate patients receiving aprepitant or fosaprepitant. Those patients <18 years of age who were admitted to the inpatient service or were seen in the pediatric infusion clinic between February 2009 and May 2012 and who received at least 1 dose of aprepitant or fosaprepitant were included. The Institutional Review Board approved the project prior to data collection. Twenty-seven patients were identified, but the exclusion of 1 patient managed at the infusion center enabled the results to focus on inpatient treatment.

Aprepitant use was evaluated for each patient (n=26) and for each cycle of chemotherapy in which the patient received aprepitant or fosaprepitant (n=114). Data included patient demographics, cancer diagnosis, types of chemotherapy including the COG regimen, indications for aprepitant use (primary prophylaxis, secondary prophylaxis, refractory nausea and vomiting), and use of rescue antiemetics. Data were not collected on the incidence of nausea and vomiting due to inconsistencies in record keeping. Chemotherapy agents were classified based on emetogenic risk using the American Society of Clinical Oncology Guidelines for Antiemetics in Oncology.⁶

RESULTS

Patient characteristics are described in Table 1. Eleven of the 26 patients (42%) were younger than 11 years of age. Six of the 26 patients (23%) weighed <20 kg, and 3 weighed <15 kg. The cancer diagnoses encompassed the broad spectrum of pediatric malignancies. The majority of patients were treated with primary prophylaxis (16 of 26 [61.5%]) for refractory nausea and vomiting (27%). Only 1 patient received aprepitant for postoperative nausea and vomiting. Twenty-six patients received a total of 287 doses of aprepitant in 114 cycles.

One patient received 5 oral doses as an outpatient in the pediatric infusion center on 5 separate cycles; this patient was excluded. Patients received an average of 4.4 cycles/patient (median of 3 cycles/patient) and an average of 11 doses/patient (median of 8.5 doses/patient). Of the

Table 1. Patient Characteristics (n=26)

Characteristic	No. of Patients (%)
Age (yr)	
<11	11 (42%)
≥11	15 (58%)
Females	14 (54%)
Weight (kg)	
10-14.99	3 (12%)
15-19.99	3 (12%)
≥20	20 (76%)
Primary tumor	
ALL	4 (15%)
AML	2 (8%)
Biphenotypic leukemia	1 (4%)
Burkett's lymphoma	1 (4%)
Ewing's sarcoma	1 (4%)
Germ cell	3 (11%)
Hodgkin's lymphoma	2 (8%)
Medulloblastoma	1 (4%)
Neuroblastoma	3 (11%)
Nonmalignant	2 (8%)
Osteosarcoma	2 (8%)
Rhabdomyosarcoma	2 (8%)
Wilms' tumor	2 (8%)
Indications	
Primary prophylaxis	16 (62%)
Secondary prophylaxis	2 (8%)
Refractory nausea and vomiting	7 (27%)
Postoperative nausea and vomiting	1 (3%)

ALL, Acute lymphoblastic leukemia; AML, acute myelogenous leukemia

287 doses administered, 197 (69%) were given as capsules, 72 (25%) as the oral liquid, and 18 (6%) as an IV infusion. Seven patients, ranging in age from 13 to 17 years old (median, 14), received IV doses of fosaprepitant over 10 cycles. Intravenous doses were given as either 115 mg or 150 mg, reflecting the change in product availability in 2011; hence, all IV doses were excluded in the analysis of duration of therapy.

Duration of therapy ranged from 1 to 10 days per cycle, with the majority of courses lasting either 1 day (31 of 104 [30%]) or 3 days (29 of 104 [28%]). Twenty-four of the 104 courses (23%)

Figure. Number of consecutive days of aprepitant administration in each course of antiemetic treatment.

exceeded the recommended 3-day course of therapy; however, 21 of the 24 courses were given to patients who received >3 days of chemotherapy. The duration of courses of aprepitant is shown in the Figure.

Our practice is to administer doses to patients <11 years of age based on body surface area (BSA); therefore, a variety of doses and dosage schemes were used. All other antiemetics were given using milligrams per kilogram. Table 2 lists the number and strength of doses given, and Table 3 provides more details about dosages for those patients <11 years old. The most frequently used doses were 125 mg and 80 mg.

Patients tolerated administration of aprepitant or fosaprepitant, and no adverse effects were reported. Only 8 patients required rescue antiemetics, suggesting that most of the patients achieved adequate control of nausea and vomiting.

DISCUSSION

CINV is a common occurrence, with as many as 60% of pediatric cancer patients reporting some type of nausea and vomiting during their chemotherapy treatment.¹¹ Despite advances in antiemetic therapies with the approval of several 5HT₃ receptor antagonists and a novel NK-1 receptor antagonist, the majority of pediatric patients continue to report CINV as one of the most feared and distressing side effects of cancer treatment.¹² Adult studies have achieved beneficial results with the addition of aprepitant to standard antiemetics such as 5HT₃ receptor antagonists and corticosteroids.

Neither aprepitant nor fosaprepitant has received approval for use in pediatric patients. Another challenge when treating younger patients is the lack of a commercially available liquid for-

Table 2. Total Number of Each Dose Administered To All Patients During the Study Period, Including Intravenous and Oral

Dose (mg)	Number of Doses
20	29
30	8
35	2
40	34
50	2
80	136
115	7
125	58
150	11
Total	287

mulation. A publication is available that reports stability of an extemporaneous preparation of aprepitant, however this remains a complicating factor that must be addressed when considering treatment for young patients.¹³

A similar single-institution retrospective analysis described aprepitant use in 32 children; however, the youngest child was only 32 months.⁹ We noted a positive experience in giving doses to children as young as 11 months and to 3 different children weighing less than 15 kg.

Information on using fosaprepitant is extremely scarce, but our review has shown that patients from 13 to 17 years old can be safely treated with IV fosaprepitant and suggests beneficial outcomes.

In patients who received >3 days of chemotherapy, we observed that aprepitant therapy can be continued beyond 3 days with no deleterious effects such as increased serum liver markers aspartate transaminase (AST) and alanine transaminase (ALT), hiccups, constipation, diarrhea, loss of appetite, and headache. Whether additional benefit is derived from this extended use has yet to be investigated. Our experience has shown that this is a well-tolerated option for CINV prophylaxis and treatment in the population of patients we reviewed.

Limitations to this analysis are the wide variability of dosages used and the nonstandardized approach to planning a course of aprepitant therapy. As a result of this review, we developed a standard weight-based dose table to be used at our institution. An investigator-initiated clinical

Table 3. Dose Details for Each Patient Under 11 Years of Age

Age (yr)	Weight (kg)	Initial dose (mg)	Subsequent doses (mg)
0.91	9.8	30	-
3	14	40	40
3	17	40	-
3	15	40	20
3	12	40	20
3	16	40	20
		50	30
5	21	40	-
6	23	50	35
6	22	40	40
10	36	125	80
10	32	40	40
		80	80
		125	80

trial is currently under way to evaluate the safety and efficacy of this dose table. Other limitations include its retrospective nature and small patient size. The retrospective design makes it difficult to ascertain whether all possible adverse effects were appropriately recorded within the chart and made assessing efficacy impractical due to inconsistencies in documentation.

CONCLUSIONS

CINV in children and adolescents represents a significant quality of life issue. With a lack of established standardized recommendations for antiemetic prophylaxis in pediatrics, practitioners must extrapolate from experiences with adult studies and incorporate what limited evidence is available in pediatric studies. There is a clear need for prospective evaluations of aprepitant and other novel antiemetic agents in pediatric patients in order to determine the most effective strategy for managing CINV in children.

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Abbreviations ALL, Acute lymphoblastic leukemia; CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; IV, intravenous; MEC, moderately emetogenic chemotherapy; NK-1, neurokinin-1

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REFERENCES

1. De Boer-Dennert M, De Wit R, Schmitz PI, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer*. 1997;76(8):1055-1061
2. Clinical Pharmacology [Internet database]. Aprepitant. Elsevier/Gold Standard, Inc.; <http://www.clinicalpharmacology.com>. Accessed: January 2, 2014.
3. Lexi-Drugs [Internet database]. Aprepitant. Lexi-Comp, Inc; <http://www.lexi.com/> Accessed: June 2, 2014
4. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. *Support Care Cancer*. 2010;18(4):423-431.
5. Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754.030 Antiemetics Trials Group. *N Engl J Med*. 1999;340(3):190-195.
6. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29(31):4189-4198.
7. Hesketh PJ. Prevention and treatment of chemotherapy-induced nausea and vomiting. UpToDate [database online]. UpToDate, Inc. http://www.uptodate.com/contents/prevention-and-treatment-of-chemotherapy-induced-nausea-and-vomiting?source=search_result&search=chemo+induced+nausea&selectedTitle=1%7E48 Accessed: January 2, 2014.
8. Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. *Pediatr Blood Cancer*. 2009;52(2):242-247.
9. Choi MR, Jiles C, Seibel NL. Aprepitant use in children, adolescents, and young adults for the control of chemotherapy-induced nausea and vomiting (CINV). *J Pediatr Hematol Oncol*. 2010;32(7):e268-271
10. Merck Sharp & Dohme Corp, NCT00818259 A multicenter, open-label, 5-part study to evaluate the pharmacokinetics, safety, and tolerability of aprepitant and fosaprepitant dimeglumine in pediatric patients receiving emetogenic chemotherapy. Clinicaltrials.gov. Accessed: January 2, 2014.
11. Holdsworth M, Raish D, Frost J. Acute and delayed nausea and emesis control in pediatric oncology patients. *Cancer*. 2006;106(4):931-940.
12. Tyc V, Mulhern R, Bieberich A. Anticipatory nausea and vomiting in pediatric cancer patients: An analysis of conditioning and coping variables. *J Dev Behav Pediatr*. 1997;18(1):27-33.
13. Dupuis LL, Lingertat-Walsh K, Walker SE. Stability of an extemporaneous oral liquid aprepitant formulation. *Support Care Cancer*. 2009;17(6):701-706.