Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial

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Summary

Background Oral aprepitant, a neurokinin-1 receptor antagonist, is recommended in combination with other anti-emetic agents for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy in adults, but its efficacy and safety in paediatric patients are unknown. We did this phase 3 trial to examine the safety and efficacy of such treatment in children.

Methods In this final analysis of a phase 3, randomised, multicentre, double-blind study, patients aged 6 months to 17 years with a documented malignancy who were scheduled to receive either moderately or highly emetogenic chemotherapy were randomly assigned with an interactive voice response system to an age-based and weight-based blinded regimen of aprepitant (125 mg for ages 12–17 years; 3·0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12–17 years; 2·0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3, or placebo plus ondansetron on day 1 followed by placebo on days 2 and 3; addition of dexamethasone was allowed. Randomisation was stratified according to patient age, planned use of chemotherapy associated with very high risk of emetogenicity, and planned use of dexamethasone as an anti-emetic. Ondansetron was dosed per the product label for paediatric use or local standard of care. The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25–120 h (delayed phase) after initiation of emetogenic chemotherapy. Efficacy and safety analyses were done with all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01362530.

Findings Between Sept 22, 2011, and Aug 16, 2013, 307 patients were randomly assigned at 49 sites in 24 countries to either the aprepitant group (155 patients) or to the control group (152 patients). Three patients in the aprepitant group and two in the control group did not receive study medication, and thus were excluded from analyses. 77 (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase (p<0·0001). The most common grade 3–4 adverse events were febrile neutropenia (23 [15%] of 152 in the aprepitant group *vs* 21 [14%] of 150 in the control group), anaemia (14 [9%] *vs* 26 [17%]), and decreased neutrophil count (11 [7%] *vs* 17 [11%]). The most common serious adverse event was febrile neutropenia (23 [15%] patients in the aprepitant group *vs* 22 [15%] in the control group).

Interpretation Addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients being treated with moderately or highly emetogenic chemotherapy.

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Introduction

Chemotherapy-induced nausea and vomiting is a frequent and potentially treatment-limiting complication of cancer therapy in both adults and children. Although effective preventive regimens have been developed in adults, data about effective regimens in children are sparse, and international treatment guidelines vary. The National Comprehensive Cancer Network guidelines have no specific age-related recommendations,[1] whereas the Multinational Association of Supportive Care in Cancer and the American Society of Clinical Oncology guidelines recommend a 5-HT_3 antagonist and dexamethasone for the prevention of acute chemotherapy-induced nausea and vomiting (ie, occurring on the day of chemotherapy) after moderately or highly emetogenic chemotherapy in children.[2,3] All three major guidelines emphasise that there are few data about neurokinin-1 receptor antagonists, such as aprepitant, in paediatric patients.[1–3]

The present standard of care (ie, a 5-HT_3 antagonist and dexamethasone) is still associated with a very high frequency of acute chemotherapy-induced nausea and vomiting in children, in excess of what is generally seen in adults.[4–6] Possible explanations for differences in children and adults might include intrinsic differences in the pathogenesis of chemotherapy-induced nausea and vomiting, differences in emetogenicity or administered doses of chemotherapy regimens, and altered exposure or

Panel 1: **Emetogenicity of commonly used chemotherapeutic agents**

Moderate (30–60% frequency)
- Cyclophosphamide (≤750 mg/m²)
- Dactinomycin (≤1·5 mg/m²)
- Doxorubicin (20–60 mg/m²)
- Estramustine
- Idarubicin
- Ifosfamide (<1·5 g/m²)
- Methotrexate (250–1000 mg/m²)
- Mitotane
- Mitoxantrone

High risk (60–90% frequency)
- Aldesleukin (>12 mU/m²)*
- Altretamine
- Amifostine (>300 mg/m²)*
- Arsenic
- Azacitidine
- Busulfan (>4 mg/kg/day as part of bone marrow transplant regimen)
- Carboplatin
- Carmustine (<200 mg/m²)
- Cisplatin (<50 mg/m²)
- Clofarabine
- Cyclophosphamide (>750 and ≤1500 mg/m²)
- Cytarabine (≥1 g/m²)
- Dactinomycin (>1·5 mg/m²)
- Dacarbazine (<500 mg/m²)
- Daunorubicin (≥45 mg/m²)
- Doxorubicin (>60 mg/m²)
- Epirubicin
- Etoposide (1800 mg/m² as part of bone marrow transplant conditioning)
- Flurouracil (>1000 mg/m²)
- Irinotecan
- Lomustine (≤60 mg/m²)
- Melphalan (intravenous; as part of bone marrow transplant)
- Methotrexate (>1000 mg/m²)
- Mitomycin (≥8 mg/m²)
- Oxaliplatin (>75 mg/m²)†
- Pentostatin
- Procarbazine

Very high risk (>90% frequency)
- Carmustine (≥200 mg/m²)
- Cisplatin (≥50 mg/m²)
- Cyclophosphamide(>1500 mg/m²)
- Dacarbazine (≥500 mg/m²)
- Ifosfamide (≥1·5 g/m²)
- Lomustine (>60 mg/m²)
- Mechlorethamine
- Streptozocin

Data from Altman[15] and Perry and colleagues.[16] *Revised or †added from National Comprehensive Cancer Network.[1]

sensitivity to anti-emetogenic regimens.[1,7] With regard to the latter, the American Society of Clinical Oncology guidelines note that higher weight-based doses of 5-HT_3 antagonists might be needed in children than in adults due to increased variability of pharmacokinetic parameters.[3] Differences in metabolic profiles, such as the known interaction between aprepitant and CYP3A4,[8] between children and adults could in theory also affect anti-emetogenic effectiveness.

Neurokinin-1 receptor antagonists have potent and usually long-lasting anti-emetic activity against a broad spectrum of central and peripheral emetic agents, whereas 5-HT_3 antagonists have a more restricted spectrum of activity with efficacy mostly against peripheral emetogens.[9–11] Brain-penetrant neurokinin-1 receptor antagonists, such as aprepitant, have shown to be clinically effective in preventing nausea and vomiting associated with emetogenic cancer chemotherapy.[12–14] Aprepitant, a potent, selective, oral neurokinin-1 receptor antagonist, in combination with a 5-HT_3 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.[8]

This study was designed to assess the efficacy and safety of oral formulations of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients aged 6 months to 17 years scheduled to be treated with moderately or highly emetogenic chemotherapy.

Methods

Study design and participants

We did a phase 3, multicentre, randomised, double-blind, active-comparator, controlled, parallel-group trial. Patients aged 6 months to 17 years with a documented malignancy (original diagnosis or relapsed) who were scheduled to receive chemotherapeutic agent(s) associated with at least a moderate (>30%) risk of emesis in the absence of prevention measures, and who were expected to receive ondansetron as part of a chemotherapy-induced nausea and vomiting preventive regimen, were included in the study. The potential emetogenic risk of chemotherapy agents was based on a five-level system that classifies commonly used chemotherapeutic agents by emetogenicity in children. This schema 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 anti-emetic treatment (panel 1). It was not possible to classify patients according to receipt of moderately or highly emetogenic chemotherapy because several chemotherapy regimens are classified on the basis of body surface area, which could not be calculated for all patients.

Major inclusion criteria were: age 6 months to 17 years at time of study entry; documented malignancy; scheduled to receive moderately emetogenic chemotherapy, highly

emetogenic chemotherapy, or very highly emetogenic chemotherapy, or chemotherapy not previously tolerated due to vomiting; patients who were scheduled to receive ondansetron as part of an anti-emetic regimen; patients aged greater than 10 years with a Karnofsky score of 60 or more; patients aged 10 years or less with a Lansky Play performance score of 60 or more; life expectancy of 3 months or more; females of childbearing potential with a negative urine pregnancy test before entering the study who agreed to use a barrier form of contraception for 14 days or more before, throughout, and for 1 month or more after the last dose of study medication; and parental or guardian consent. Major exclusion criteria were: vomiting 24 h before treatment day 1; symptomatic primary or metastatic CNS malignancy causing nausea or vomiting; known history of QT prolongation or allergic reaction to any of the study drugs; 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 aminotransferase or aspartate aminotransferase >5·0 times the upper limit of normal for age, bilirubin or serum creatinine >1·5 times the upper limit of normal for age); initiation of systemic corticosteroids within 72 h before study drug administration or as part of the chemotherapy regimen; benzodiazepines or opioids initiated within 48 h before treatment, except for single doses of triazolam, temazepam, or midazolam; use of anti-emetics within 48 h of treatment; use of CYP3A4 substrates or inhibitors within 7 days or CYP3A4 inducers within 30 days of treatment; and pregnant or breast-feeding patients.

We did the trial according to good clinical practice standards plus applicable country or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human beings participating in biomedical research. The protocol was reviewed and approved by the independent ethics committee at each participating centre, and the parent or legal guardian of each patient provided written informed consent. Additionally, patients aged 12–17 years, or as required by local regulations, provided assent.

Randomisation and masking

Patients who satisfied all study entry criteria were randomly assigned (1:1) to the aprepitant group or the control group by an interactive voice response system with a stratified randomised block design. The biostatistical department at Merck & Co., Inc. generated the allocation schedule using a computerised generating system; this was done by an individual not involved in the data analysis. The schedule was then provided to the interactive voice response system that randomly assigned patients on the basis of the supplied schedule.

	Day 1	Day 2	Day 3
Patients aged 12–17 years			
Aprepitant regimen	125 mg capsule orally plus ondansetron*	80 mg capsule orally	80 mg capsule orally
Control regimen	Placebo + ondansetron	Placebo	Placebo
Patients aged 6 months to less than 12 years			
Aprepitant regimen	Powder for suspension 3·0 mg/kg (up to 125 mg) plus ondansetron*	Powder for suspension 2·0 mg/kg (up to 80 mg)	Powder for suspension 2·0 mg/kg (up to 80 mg)
Control regimen	Placebo plus ondansetron	Placebo	Placebo

*Branded ondansetron was given according to product label for paediatric use or according to local standard of care.

Table 1: **Treatment regimens**

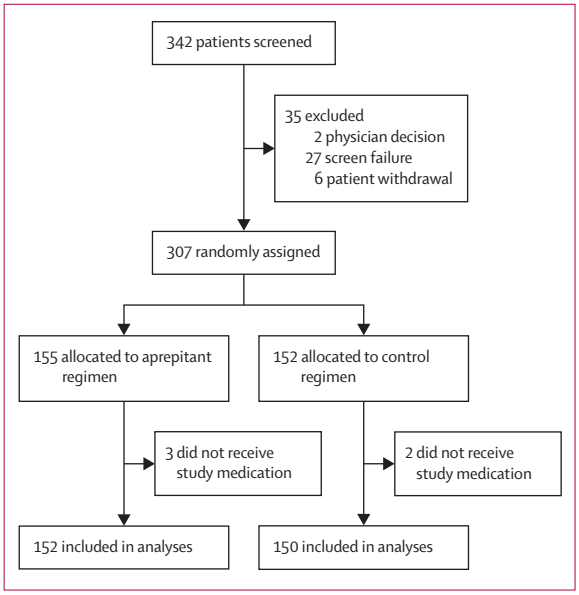

Figure 1: **Trial profile**

Randomisation was stratified based on patient age (6 months to <2 years, 2 to <6 years, 6 to <12 years, or 12 to 17 years), planned use of chemotherapy associated with a very high risk (>90%) of emetogenicity, and planned use of dexamethasone as an anti-emetic. Aprepitant and matching placebo were supplied in a masked manner as capsules for patients aged 12–17 years and as sachets of a novel oral powder for suspension formulation for patients aged less than 12 years.

All participants and study-site personnel were masked to treatment except the pharmacist at each site, who needed to prepare the study medication. Any premature unmasking of a participant would be noted in the interactive voice response system and an alert would be sent to the sponsor. The sponsor database was masked to all sponsor personnel except for one unmasked clinical scientist who could access the unmasked data to ensure proper dosing. The unmasked data were not available to sponsor personnel until the database was locked at the end of the study.

Procedures

Patients randomly allocated to the aprepitant group received aprepitant plus ondansetron, while those assigned to the control group received placebo plus ondansetron. The dose of aprepitant differed for patients aged 6 months to less than 12 years and for patients aged 12 to 17 years (table 1). Aprepitant was given 60 min before initiation of chemotherapy on day 1, and in the morning on days 2 and 3. For patients receiving chemotherapy on day 2 or 3, aprepitant was given 60 min before chemotherapy. The dose of ondansetron was selected at the investigator's discretion according to the product label for paediatric usage or local standard of care. In addition to day 1 dosing, ondansetron was permitted as prophylactic treatment on other days that chemotherapy was given. The starting dose of ondansetron was given no later than 30 min before starting chemotherapy. Intravenous dexamethasone could be added to either treatment regimen at the investigator's discretion, with the starting dose given no later than 30 min before starting chemotherapy. When given in combination with aprepitant, dexamethasone doses were reduced by 50% in a masked manner (prepared and given by different unmasked site personnel). A 50% dexamethasone dose reduction was extrapolated from adult pharmacokinetic data because there are few data about pharmacokinetic interactions in children.[17,18] Standard doses of rescue medication (5-HT_3 antagonists, phenothiazines, butyrophenones, benzamides, corticosteroids, benzodiazepines, and domperidone) were permitted to alleviate established nausea or vomiting (ie, not prophylactically). A list of permitted rescue medications was provided, but the specific medication and dose was left to the discretion of the investigator.

Although the main focus of this analysis was on the single double-blind cycle of aprepitant (cycle 1), the study design allowed for up to five subsequent cycles of open-label aprepitant.

The doses of aprepitant used were established as follows. For paediatric patients aged 6 months to less than 12 years, we developed a population pharmacokinetics model based on data from a phase 1 study of aprepitant for the treatment of chemotherapy-induced nausea and vomiting in paediatric patients (ClinicalTrials.gov, number NCT00818259), which assessed an oral aprepitant powder for suspension formulation at various doses and regimens. Data from this study are shown in the appendix. We modelled paediatric dose adjustments using all available data to approximate pharmacokinetic parameters associated with safe and efficacious dosing for chemotherapy-induced nausea and vomiting in adults using the approved dosing regimen of 125 mg on day 1 and 80 mg on days 2 and 3.[8] Based on the simulations, 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 6 months to less than 12 years, using the paediatric formulation. Aprepitant powder for suspension was given as a homogeneous suspension in water at a concentration of 25 mg/mL; the desired dose, calculated based on bodyweight, was drawn into a syringe and given orally.

Pharmacokinetic data from a phase 3 study in which adolescents received the approved 3 day oral aprepitant capsule regimen for adults (ClinicalTrials.gov, number NCT00080444) showed that, although plasma concentrations of aprepitant were consistently lower in

See Online for appendix

	Aprepitant group (n=152)	Control group (n=150)
Age (years)	7·2 (0·5–17·8)	7·6 (0·5–17·8)
Age group		
6 months to <2 years	19 (13%)	16 (11%)
2 to <6 years	45 (30%)	43 (29%)
6 to <12 years	41 (27%)	43 (29%)
12 to 17 years	47 (31%)	48 (32%)
Sex		
Male	84 (55%)	79 (53%)
Female	68 (45%)	71 (47%)
Ethnic origin		
White	119 (78%)	110 (73%)
Asian	11 (7%)	16 (11%)
Other	22 (14%)	24 (16%)
Weight (kg)	24·0* (6·7–103·9)	26·8† (6·0–134·8)
Receipt of previous chemotherapy	89 (59%)	90 (60%)
Receipt of very highly emetogenic chemotherapy	99 (65%)	101 (67%)
Ondansetron therapy‡	152 (100%)	150 (100%)
Dose (mg/kg)	0·18 (0·08–0·89)	0·17 (0·06–0·95)
Use of dexamethasone§	42 (28%)	44 (29%)
Dose (mg/kg)	0·08 (0·2–0·19)	0·15 (0·05–0·44)
Most common primary malignancies¶		
Ewing's sarcoma	17 (11%)	16 (11%)
Osteosarcoma	17 (11%)	16 (11%)
Neuroblastoma	13 (9%)	11 (7%)
Acute lymphocytic leukaemia	13 (9%)	8 (5%)
Rhabdomyosarcoma	12 (8%)	13 (9%)
Medulloblastoma	9 (6%)	12 (8%)
Nephroblastoma	8 (5%)	7 (5%)
Most frequently used chemotherapy agents‖		
Vincristine sulphate	65 (43%)	73 (49%)
Etoposide	57 (38%)	54 (36%)
Ifosfamide	45 (30%)	48 (32%)
Doxorubicin	45 (30%)	44 (29%)
Carboplatin	39 (26%)	27 (18%)
Cisplatin	35 (23%)	39 (26%)
Cyclophosphamide	31 (20%)	33 (22%)
Methotrexate	23 (15%)	23 (15%)
Dactinomycin	17 (11%)	15 (10%)

Data are median (range) or n (%). *n=149. †n=148. ‡Mean duration of ondansetron therapy was 3·0 and 2·8 days in the aprepitant and control groups, respectively. §Mean duration of dexamethasone therapy was 3·1 and 3·0 days in the aprepitant and control groups, respectively; dexamethasone doses were reduced by 50% in a masked manner when given in combination with aprepitant. ¶Defined as those reported in 5% or more of patients. ‖Defined as those used in 10% or more of patients.

Table 2: **Baseline characteristics of treated patients**

adolescents than in adults, the differences were not significant.[19] With an estimated neurokinin-1 receptor occupancy of greater than 90% throughout the 3 day regimen, no further adjustment of aprepitant dose was considered necessary in adolescents.

Episodes of vomiting or retching, or use of rescue medication, or both, were recorded in a paper diary during the efficacy assessment period (0–120 h after initiation of chemotherapy). The date and time of each vomiting episode were recorded by patients, their parents, or guardians at the time of occurrence, and parents or guardians recorded the name, date, and time of any rescue medication given. A vomiting episode was defined as one or more episodes of emesis (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents), with distinct vomiting episodes defined as being separated by the absence of emesis or retching for 1 min or more.

Vital signs and adverse events were recorded at all study visits, and laboratory tests (haematology, chemistry, and urinalysis) and 12-lead electrocardiography were done within 7 days before initiation of study medication, after treatment (days 6–8), and at follow-up or discontinuation (days 19–29, or immediately before the next round of chemotherapy). Patients and their parents or guardians were instructed to notify the investigators immediately of any adverse events, and patients were questioned about adverse events during study visits. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (version 4).[20] Vomiting was reported as an adverse event only if the vomiting episode occurred outside of the efficacy assessment period or the vomiting met criteria for a serious adverse event.

Compliance with diary completion was checked via telephone contact on all diary days, and compliance with study medication was assessed by pill or sachet count at the post-treatment visit.

Patients could withdraw from the trial at any time or be withdrawn at the discretion of the investigator if untoward effects occurred. Patients could also be withdrawn for protocol violations, and for administrative or safety reasons.

Outcomes

The primary efficacy endpoint was the proportion of patients who achieved a complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25–120 h (delayed phase) after initiation of emetogenic chemotherapy. The primary efficacy endpoint was chosen in consultation with the US Food and Drug Administration because this was considered to be the phase in which treatment would have the most benefit. Secondary efficacy endpoints were the proportion of patients who achieved complete response during the acute (0–24 h) and overall phases (0–120 h), and no vomiting (regardless of rescue medication use) during the acute, delayed, and overall phases. Nausea was assessed indirectly by incidence of vomiting and use of rescue medication given the difficulty to assess this reliably in children. Safety and tolerability of the anti-emetic regimens were also assessed.

Statistical analysis

With about 150 patients per treatment group, the study had 80% power to show superiority of aprepitant over control in the proportion of patients achieving a complete response during the delayed phase with a one-sided alpha of 0·025. We assumed an overall dropout rate of 3%, response of 60% for the control group, and an underlying treatment difference of 15 percentage points between treatment groups.

We compared treatments for the efficacy endpoints using the Cochran-Mantel-Haenzel test stratified by age group, use of dexamethasone as an anti-emetic, and receipt of very highly emetogenic chemotherapy. We calculated descriptive statistics for demographic variables and baseline characteristics, as well as for the proportion of patients who achieved complete response by age group, the proportion of patients experiencing vomiting by number of episodes, and the proportion of patients with no use of rescue medication. We prepared Kaplan-Meier curves showing the percentage of patients who did not use rescue medication (for the exploratory analyses of time to first use of rescue medication) and the percentage of patients who were free of vomiting since the initiation of emetogenic chemotherapy (for the exploratory analyses of time to first vomiting episode), with log-rank tests for the treatment comparisons. In prespecified, but exploratory analyses, we compared the proportion of patients who achieved complete response in patients aged less than 12 years with those aged 12–17 years. We compared the proportion of patients who achieved complete response by dexamethasone use or non-use,

	Aprepitant group (n=152)	Control group (n=150)	p value
Complete response			
Acute phase	101 (66%)	78 (52%)	0·0135
Delayed phase	77 (51%)	39 (26%)	<0·0001
Overall phase	61 (40%)	30 (20%)	0·0002
No vomiting			
Acute phase	108 (71%)	80 (53%)	0·0023
Delayed phase	84 (55%)	42 (28%)	≤0·0001
Overall phase	71 (47%)	32 (21%)	≤0·0001
No use of rescue medication			
Acute	133 (88%)	115 (77%)	..*
Delayed	110 (72%)	81 (54%)	..*
Overall	101 (66%)	73 (49%)	..*

Data are n (%). *Not calculated.

Table 3: **Proportion of patients achieving efficacy endpoints (intention-to-treat population)**

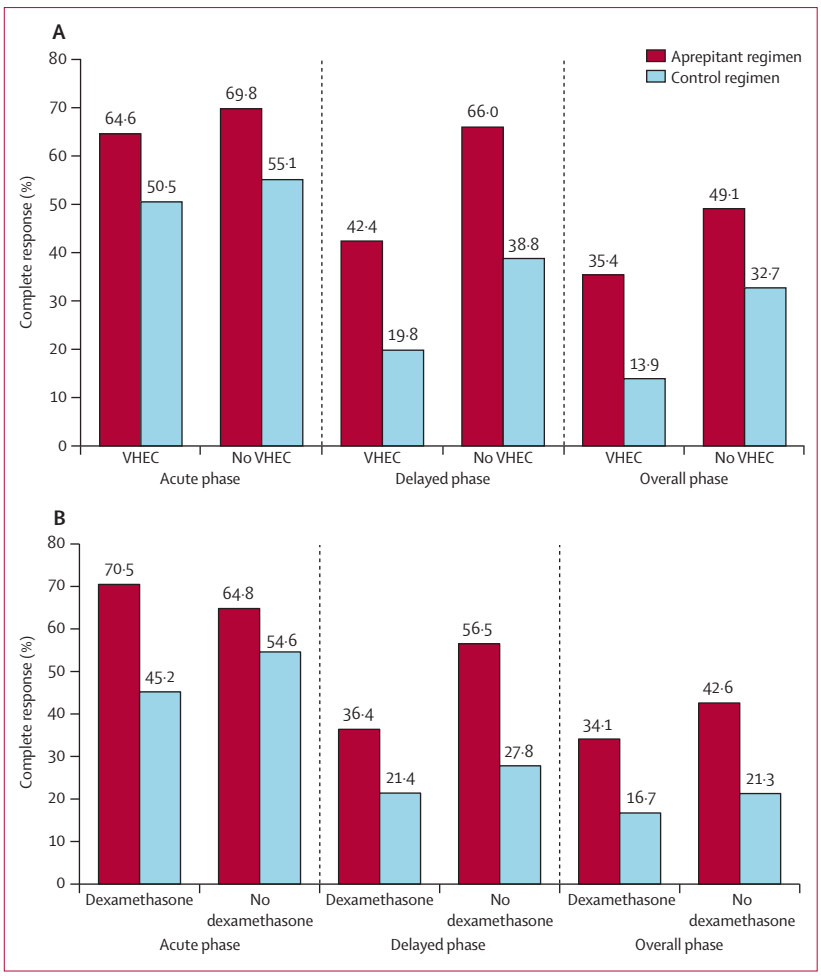

Figure 2: **Proportion of patients who achieved a complete response with (A) very highly emetogenic chemotherapy and (B) dexamethasone use**

Complete response=no vomiting, no retching, and no use of rescue medication. VHEC=very highly emetogenic chemotherapy.

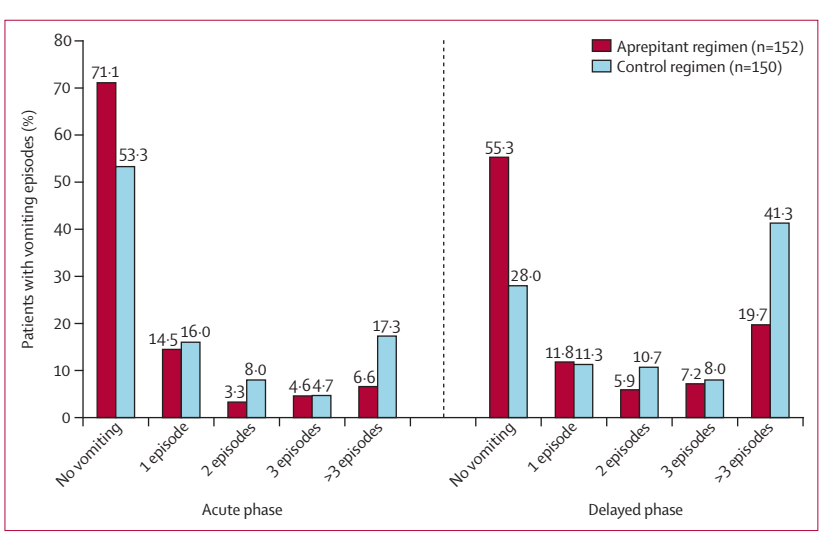

Figure 3: **Patients experiencing vomiting episodes in the acute and delayed phases**

and very highly emetogenic chemotherapy use or non-use in each of the phases (acute 0–24 h, delayed 25–120 h, and overall 0–120 h) after initiation of chemotherapy.

For adverse events with at least four patients in any treatment group having the same event, point estimates and 95% CIs were calculated for between-group comparisons; for all other adverse events, only point estimates by treatment group were calculated. The 95% CIs for between-group differences in adverse events were calculated by the Miettinen and Nurminen method.[21]

Efficacy and safety analyses were done with all randomised patients who received at least one dose of study treatment. All analyses were done using SAS (version 9.1).

The study is registered at ClinicalTrials.gov, number NCT01362530.

Role of the funding source

Merck & Co., Inc. funded this study, and was responsible for the study design, conduct, data collection, and analysis. SL, AT, CDC, and SG had access to the raw data. All authors had access to study data tables, participated in data analysis and interpretation, and had final responsibility for the decision to submit for publication. Writing and editorial assistance were funded by the study sponsor and were done under the direction of the authors.

Results

Between Sept 22, 2011, and Aug 16, 2013, 342 patients were screened. 307 of these were randomly assigned at 49 sites in 24 countries (appendix). Reasons for exclusion are shown in figure 1. Among the randomly assigned patients, three in the aprepitant group and two in the control group did not receive study medication, so were excluded from efficacy and safety analyses. One patient could not swallow the study medication and withdrew from the study; two patients were randomly assigned but did not receive study medication because they no longer met study entry criteria (vomiting within 24 h before treatment day 1 and excluded medication); one patient discontinued before study medication was given; and one patient was randomly assigned in error. Baseline characteristics of the 302 patients who received at least one dose of study drug are shown in table 2. The median patient age was 7·5 years (range 6 months to 17·8 years). Baseline demographics were similar between treatment groups. In general, treatment groups were balanced with regard to primary malignancies and the type and emetogenicity of administered chemotherapy agents. The most frequently used chemotherapy agents were vincristine sulphate, etoposide, ifosfamide, and doxorubicin (table 2), with most patients receiving chemotherapy for 3 days (range 1–7). 126 (83%) of 152 patients in the aprepitant group and 134 (89%) of 150 patients in the control group received chemotherapy for more than 1 day. The proportion of patients receiving

very highly emetogenic chemotherapy and the proportion of patients who received dexamethasone were similar between the aprepitant and control groups (table 2).

147 (97%) of 152 patients in the aprepitant group and 147 (98%) of 150 patients in the control group completed the chemotherapy cycle. Reasons for discontinuation in the aprepitant group were adverse events (two), protocol violation (two), and patient withdrawal (one). Reasons for discontinuation in the control group were patient withdrawal (two) and physician decision (one). Only one patient in the control group was not 100% compliant with their study medication, receiving two of the three doses of control treatment.

77 (51%) of 152 patients in the aprepirant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase (p<0·0001; table 3). Complete response during the acute and overall phases was also more common in patients in the aprepitant group than in those who were in the control group (table 3).

An exploratory analysis examined whether the proportion of patients who achieved a complete response in the delayed phase was independent of the proportion of patients who achieved a complete response in the acute phase. The proportion of patients who achieved a complete response in the delayed phase in the aprepitant group was higher than in the control group regardless of response in the acute phase (data not shown). A supportive logistic regression analysis, which included terms for treatment, dexamethasone use, receipt of very highly emetogenic chemotherapy, and age group, confirmed the findings for the delayed, acute, and overall phases (all p<0·05; data not shown). The proportions of patients who achieved a complete response across all phases were higher in the aprepitant group than the control group regardless of the use of very highly emetogenic chemotherapy or use of dexamethasone (figure 2).

The proportion of patients with no vomiting and the proportion of patients with no use of rescue medication were also greater in the aprepitant group than in the control group in all phases (table 3, figure 3). Median time to first vomiting episode was 96·3 h (95% CI 68·8–not estimable) in the aprepitant group and 27·5 h (95% CI 19·3–35·6) in the control group (log-rank p<0·0001; figure 4). Similarly, time to first rescue medication use was significantly longer for patients in the aprepitant group than in the control group (figure 5; log-rank p=0·0024). At 98 h, 68% (95% CI 60·3–75·2) of patients in the aprepitant group and 52% (44·3–60·4) in the control group were free of rescue medication use.

The proportion of patients achieving a complete response was similar for patients aged less than 12 years who received the powder for suspension formulation and for those aged 12–17 years who received capsules in the overall phase (43 [41%] of 105 *vs* 18 [38%] of 47) and delayed phase (53 [50%] of 105 *vs* 24 [51%] of 47), and higher for the younger group than the older group in the acute phase (75 [71%] of 105 *vs* 26 [55%] of 47).

Adverse events were reported by 120 (79%) of 152 patients in the aprepitant group and 116 (77%) of 150 in the control group, with small differences between the treatment regimens for any of the adverse event summary categories (table 4). In addition to vomiting, the most commonly reported all-grade adverse events

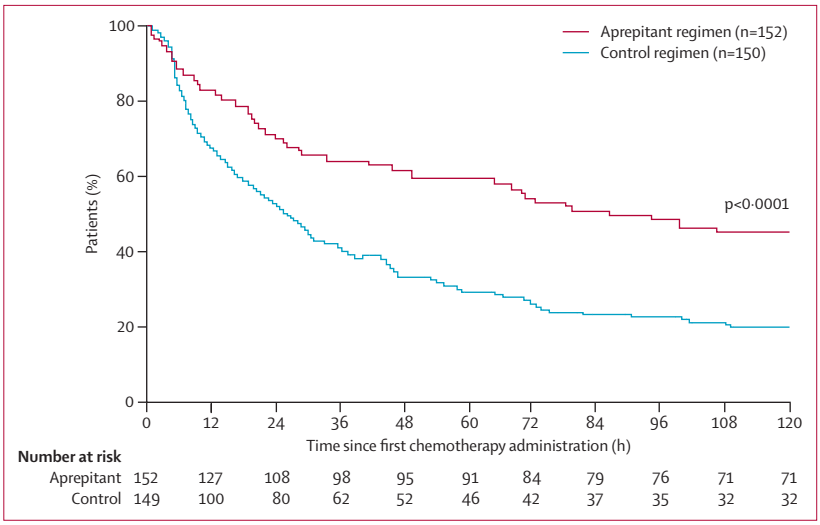

Figure 4: **Time to first vomiting episode**

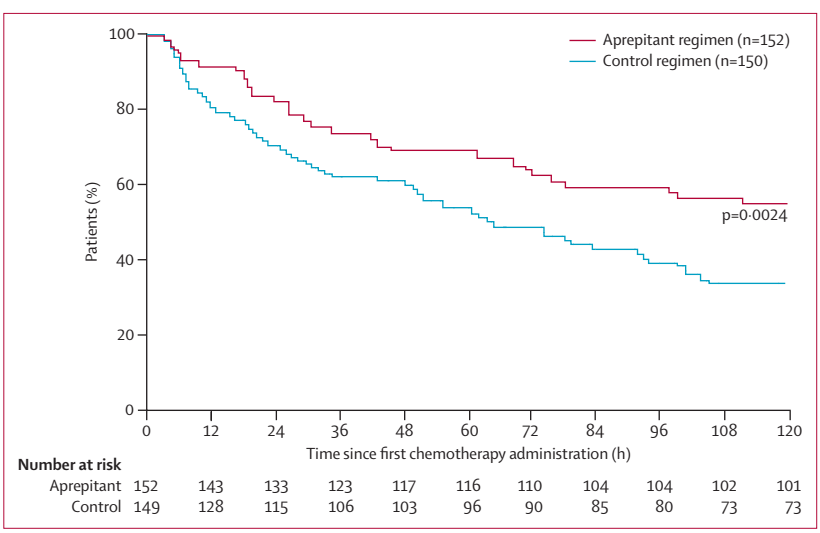

Figure 5: **Time to first rescue medication use**

	Aprepitant group (n=152)	Control group (n=150)	Treatment difference (95% CI)
One or more	120 (79%)	116 (77%)	1·6 (−7·8 to 11·0)
Drug-related	5 (3%)	3 (2%)	1·3 (−2·8 to 5·7)
Serious	46 (30%)	41 (27%)	2·9 (−7·3 to 13·1)
Serious drug-related	2 (1%)	0	1·3 (−1·2 to 4·7)

Table 4: **Overall adverse event profile**

	Aprepitant group (n=152)				Control group (n=150)			
	Grades 1–2	Grade 3	Grade 4	All Grades	Grades 1–2	Grade 3	Grade 4	All Grades
Febrile neutropenia	1 (<1%)	19 (13%)	4 (3%)	24 (16%)	3 (2%)	17 (11%)	4 (3%)	24 (16%)
Anaemia	10 (7%)	12 (8%)	2 (1%)	26 (17%)*	12 (8%)	25 (17%)	1 (<1%)	38 (25%)
Neutropenia	6 (4%)	7 (5%)	7 (5%)	21 (14%)†	3 (2%)	7 (5%)	8 (5%)	18 (12%)
Neutrophil count decrease	2 (1%)	3 (2%)	8 (5%)	13 (9%)	2 (1%)	3 (2%)	14 (9%)	19 (13%)
Platelet count decrease	2 (1%)	6 (4%)	4 (3%)	12 (8%)	5 (3%)	5 (3%)	5 (3%)	15 (10%)
Thrombocytopenia	11 (7%)	3 (2%)	1 (<1%)	15 (10%)	3 (2%)	7 (5%)	6 (4%)	16 (11%)
Vomiting	19 (13%)	3 (2%)	1 (<1%)	23 (15%)	18 (12%)	4 (3%)	1 (<1%)	23 (15%)
Nausea	12 (8%)	0	1 (<1%)	13 (9%)	16 (11%)	1 (<1%)	0	17 (11%)

Data are n (%). Adverse events graded according to National Cancer Institute Common Toxicity Criteria (version 4). *Includes two reports of unknown grade. †Includes one report of unknown grade.

Table 5: **Adverse events reported in 10% or more of patients**

Panel 2: Research in context

Systematic review

Several cancer guidelines (National Comprehensive Cancer Network, Multinational Association of Supportive Care in Cancer, and the American Society of Clinical Oncology) have noted few data about use of neurokinin-1 receptor antagonists such as aprepitant in the paediatric population. Although a systematic review was not done before initiation of the study, we did search PubMed for clinical trials published between Jan 1, 1995, and March 1, 2014 using the search terms "aprepitant", "paediatric", and "chemotherapy", revealing only small clinical or observational studies with very few participants and consequently no large, randomised, placebo-controlled trials assessing aprepitant for chemotherapy-induced nausea and vomiting in paediatric patients.

Interpretation

To the best of our knowledge, this is the first large, randomised, phase 3 study assessing aprepitant in the paediatric population. A 3 day regimen of aprepitant combined with ondansetron was well tolerated and resulted in a higher proportion of patients achieving a complete response (no vomiting with no use of rescue medication) across all three phases (acute, delayed, and overall). The findings from this study suggest that the addition of aprepitant to anti-emetic therapy might be effective in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients treated with a moderately or highly emetogenic chemotherapy regimen.

were anaemia, febrile neutropenia, and neutropenia (table 5). The most common grade 3–4 adverse events reported were febrile neutropenia, anaemia, and neutrophil count decrease (table 5), all of which occurred with a similar frequency in both treatment groups, except for anaemia, which was reported by more patients in the control group than in the aprepitant group (table 5). Additional grade 3 adverse events not included in table 5 were pyrexia (one patient in the control group), diarrhoea (one patient in the control group), leukopenia (one patient in the aprepitant group; five patients in the control group), and decreased haemoglobin (six patients in each group). Additional grade 4 adverse events occurred in two patients in the control group (one each with leukopenia and diarrhoea).

Serious adverse events were reported in 87 patients overall (table 4). The most common serious adverse event was febrile neutropenia, reported in 23 (15%) of 152 patients in the aprepitant group and 22 (15%) of 150 patients in the control group. Overall, the incidence of serious adverse events was similar between treatment groups and was typical of a patient population receiving chemotherapy. Two patients in the aprepitant group discontinued aprepitant due to a serious adverse event (allergic reaction to carboplatin and anaphylactic shock due to etoposide). No treatment-related deaths occurred.

Five (3%) of the 152 patients in the aprepitant group and three (2%) of the 150 patients in the control group had adverse events determined by the investigator to be related to study medication (aprepitant or ondansetron). These were hiccups, *Clostridium difficile* infection, vomiting, constipation, blood calcium and potassium concentrations decreased, and electrocardiogram T-wave inversion in the aprepitant group; and increased alanine and aspartate aminotransferase levels (two each), and nausea in the control group. Two of the treatment-related events (*C difficile* infection and electrocardiogram T-wave inversion), both in the aprepitant group, were considered treatment-related serious adverse events. No unexpected serious adverse reactions were reported.

Discussion

Overall, results from this study show that a 3 day age-adjusted and weight-adjusted oral aprepitant regimen, in combination with ondansetron with or without 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. The proportion of patients who

achieved a complete response was higher in the aprepitant group than in the control group across all three phases (acute, delayed, and overall; panel 2).

The proportion of patients who achieved a complete response was lower for patients who received dexamethasone than for those who did not, particularly in the delayed and overall phases. Because the use of dexamethasone was mandated by the investigator, there might have been a potential bias towards poorer outcomes when dexamethasone was used because patients with the greatest prior emesis or those receiving the most difficult regimens might have been selected to receive dexamethasone. However, the proportion of patients who achieved a complete response with the aprepitant regimen than with the control regimen was higher across all phases, irrespective of dexamethasone use.

Based on previous pilot pharmacokinetic and clinical data,[19] adolescents aged 12–17 years received the adult regimen consisting of 125 mg on day 1 and 80 mg on days 2 and 3. For children aged 6 months to less than 12 years, the doses given in this study were modelled from phase 1 data. Based on initial simulations, body-weight-based dosing of 3·0 mg/kg on day 1 with 2·0 mg/kg on days 2 and 3 appeared to approximate the pharmacokinetic exposures seen in adults. Although no pharmacokinetic data were obtained in the present study, this approach was validated clinically in that the proportion of patients who achieved a complete response were generally similar between patients aged less than 12 years who were given aprepitant powder for suspension and those aged 12–17 years who were given aprepitant capsules. This result is especially important since one of the most important considerations during the development of specific paediatric formulations is accurate measurement of dose and ease of administration.[22]

Although the addition of aprepitant to the standard of care improved control of chemotherapy-related nausea and vomiting, the proportions of patients achieving a complete response in this study were lower than those seen in studies of adults receiving moderately or highly emetogenic chemotherapy (aprepitant regimen: acute phase, 83–89%; delayed phase, 68–80%; overall phase, 51–73%; control regimen: acute phase, 68–78%; delayed phase, 47–63%; overall phase, 43–61%).[8,12,13,23,24] Possible reasons for this might be different emetogenicity, higher chemotherapy doses, and different combinations of chemotherapeutic agents between the two populations.[19] Furthermore, in many anti-emetic studies done in adults, patients had been chemotherapy-naive or had not received many days of chemotherapy.[12–14,24] By contrast, in the present study, most patients had received chemotherapy before and had many days of chemotherapy treatment. Despite the lower absolute response observed in the present study versus historical data in adults, aprepitant still represents a clinically significant advancement in the paediatric and adolescent patient population, in which there is medical need for better prevention of nausea and vomiting.[2]

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 aprepitant 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 anti-emetic regimens is needed.

This study has several limitations. Although the study allowed for individualised treatment, the use of rescue medications was not controlled for (ie, investigator-determined), which might have affected the results. Additionally, although the results of the study were generally consistent for the broad categories of both very highly emetogenic chemotherapy and not very highly emetogenic chemotherapy regimens, the study was not designed to assess the efficacy of aprepitant for individual chemotherapy regimens.

In conclusion, our findings suggest that the addition of aprepitant to ondansetron with or without dexamethasone might be effective in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients being treated with moderately or highly emetogenic chemotherapy regimens.

Contributors

SG, SL, AT, and CDC substantially contributed to the conception and design of the study. CMZ, HJK, SL, AT, and CDC were responsible for data acquisition. All authors participated in the data analysis and interpretation. All authors reviewed and provided input on the outline and manuscript drafts, and provided final approval for manuscript submission.

Declaration of interests

HJK and CMZ declare no competing interests. SL, AT, and CDC are employees of Merck & Co., Inc. SG is an employee and stockholder of Merck & Co., Inc.

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