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ORIGINAL RESEARCH

Antiemetic Prophylaxis with Fosaprepitant and 5-HT_3-Receptor Antagonists in Pediatric Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

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Background: High-dose myeloablative conditioning prior to autologous hematopoietic stem cell transplantation (autoHSCT) in pediatric patients is usually highly emetogenic. The antiemetic neurokinin-1 receptor antagonist fosaprepitant was safe and effective in children receiving highly emetogenic chemotherapy. Data on fosaprepitant during autoHSCT in children are currently not available.

Methods: A total of 35 consecutive pediatric patients, who received an antiemetic prophylaxis with fosaprepitant (4 mg/kg; single dose, max. 1 x 150 mg/kg BW) and ondansetron (24-hours continuous infusion; 8–32 mg/24h) or granisetron (2 x 40 µg/kg·d^{-1}) during highly emetogenic conditioning chemotherapy before autoHSCT were retrospectively analyzed, and their results were compared with a control group comprising 35 consecutive pediatric patients, who received granisetron or ondansetron only. The antiemetic efficacy and the safety of the two prophylaxis regimens were compared with respect to three time periods after the first chemotherapy administration (0–24h, >24–120h, >120–240h).

Results: Clinical adverse events and clinically relevant increases/decreases of laboratory markers were similarly low and did not significantly differ between the two study groups ($p>0.05$). The registered number of vomiting events was significantly higher in the control group in the time periods of 0–24h (64 vs 22 events; $p<0.01$), >24–120h (135 vs 78 events; $p<0.0001$), >120–240h (268 vs 105 events; $p<0.0001$), and the whole observation period 0–240h (467 vs 205 events; $p<0.0001$). The percentage of patients experiencing vomiting was higher in the control group during the time period of >24–120h (100% vs 74.3%) but not the other analyzed time periods ($p>0.05$).

Conclusion: The fosaprepitant-based antiemetic prophylaxis was safe, well tolerated and significantly reduced vomiting in children undergoing highly emetogenic chemotherapy prior to autoHSCT. Prospective randomized trials are necessary to confirm these results.

Keywords: fosaprepitant, 5-HT_3-antagonists, pediatric, antiemetic prophylaxis, chemotherapy-induced nausea and vomiting, autologous hematopoietic stem cell transplantation

Introduction

The autologous hematopoietic stem cell transplantation (autoHSCT) is a standard curative treatment for pediatric solid tumors such as neuroblastoma and Ewing's sarcoma, and it is also regularly used for treating specific relapsed or high-risk solid tumors including Hodgkin's lymphoma, medulloblastoma, osteosarcoma, retinoblastoma, primitive neuroectodermal tumors (PNET), rhabdoid tumors or germ cell tumors in

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children.[1–8] In Germany, autoHSCT was performed on average 78 times per year between 2013 and 2018.[9] Conditioning chemotherapy protocols prior to autoHSCT are highly dosed and myeloablative and therefore require a comprehensive supportive care, including an effective antiemetic prophylaxis. Since the conditioning chemotherapy usually comprises highly emetogenic agents that are repeatedly administered over several consecutive days, chemotherapy-induced nausea and vomiting (CINV) is a difficult side effect to control in this therapy setup. Besides its usually severe impairment in terms of quality of life, CINV may have a major impact on nutritional condition, electrolyte imbalances, and severity of mucositis.[10] Despite the development of comprehensive antiemetic prophylaxis regimens, complete control of CINV (complete absence of nausea, retching and vomiting) is rarely achieved in pediatric patients undergoing allogeneic or autologous HSCT.[11]

In 2018, the water-soluble neurokinin-1 (NK_1) receptor antagonist fosaprepitant was approved for pediatric patients between 0.5 and 17 years of age by the European Medicines Agency and the US Food and Drug Administration.[12,13] Current international supportive care guidelines recommend an antiemetic prophylaxis with a 5-HT_3-receptor antagonist (eg ondansetron, granisetron), dexamethasone, and the NK_1-receptor antagonist aprepitant for children receiving highly emetogenic chemotherapy.[14,15]

Prophylaxis regimens with 5-HT_3-receptor antagonists with or without dexamethasone and fosaprepitant were safe and effective in pediatric and adult patients receiving highly emetogenic chemotherapy.[16–23] At present there is no study data available that analyzed the use of fosaprepitant in pediatric patients undergoing highly emetogenic conditioning chemotherapy prior to autoHSCT.

In this retrospective study, the safety and efficacy of the antiemetic prophylaxis regimen with single-dose intravenous fosaprepitant in addition to a 5-HT_3-receptor antagonist (ondansetron or granisetron) were analyzed and evaluated in pediatric patients (0.5–17 years of age) undergoing highly emetogenic chemotherapy before autoHSCT. The results were compared with a control cohort receiving a standard antiemetic prophylaxis regimen with ondansetron or granisetron only.

Materials and Methods

Study Background and Design

In 2016, the standard antiemetic prophylaxis regimens used during autoHSCT of the two study sites at University Children's Hospital Tübingen and Dr. von Hauner Children's Hospital Munich, Germany were gradually complemented with single-dose fosaprepitant directly before starting the conditioning chemotherapy. Initially, older patients >12 years of age received fosaprepitant. Then, with increasing experience and further upcoming study data on fosaprepitant in children, the regimen was changed in younger children, as well.

In order to evaluate the safety and antiemetic efficacy of fosaprepitant in pediatric patients undergoing autoHSCT, we analyzed data of 35 consecutive patients (autoHSCT between 2016 and 2019; fosaprepitant group) and compared them with a control group of 35 patients (control group) who received the standard antiemetic prophylaxis regimen only (autoHSCT between 2013 and 2016). Data of the fosaprepitant group including demographics, blood tests, clinical factors such as vomiting events, medication, adverse events, and survival were prospectively monitored and abstracted from the patient records. Data of the control group were retrospectively analyzed.

The inclusion criteria were being aged between 0.5 and < 18 years at the time of autoHSCT, undergoing highly emetogenic conditioning chemotherapy prior to autoHSCT (as defined by[24]), and the administration of an antiemetic prophylaxis regimen comprising granisetron/ondansetron only (control group) or granisetron/ondansetron and fosaprepitant (fosaprepitant group). Antiemetic on-demand medication with dimenhydrinate, metoclopramide intravenously or levomepromazine 24-hour continuous intravenous infusion for the treatment of breakthrough nausea and vomiting was allowed.

The exclusion criteria were the use of antiemetic drugs or vomiting in the preceding 24 hours before starting the conditioning chemotherapy, the use of dexamethasone during the conditioning chemotherapy, and the administration of other antiemetic drugs than those listed above during the conditioning chemotherapy and the observation period.

The observation period was defined as the time between the first administration of a highly emetogenic agent of the conditioning chemotherapy (control group) or the administration of fosaprepitant directly before starting the conditioning chemotherapy (fosaprepitant group) until 240 hours (h) thereafter. The observation period was divided into three time periods: 0–24h, >24–120h, and >120h–240h. The efficacy analyses were compared between the two study groups with respect to these three time periods and/or the whole observation period. The safety analyses were compared

between the two study groups with respect to the whole observation period.

Drug Administration

All antiemetic drugs were intravenously administered (central venous catheter or Hickman-catheter).

Patients of the University Children's Hospital Tübingen received granisetron (2 x 40 microgram per kilogram bodyweight (µg per kg BW) and day, with a maximum of 2 x 3 milligram (mg) per day) during the whole conditioning period as a slow intravenous (IV) injection within 3 minutes. The first dose was administered at least 30 minutes before starting the conditioning chemotherapy. Granisetron was administered through the whole conditioning period until 24h after the last administration of a chemotherapeutic agent.

Patients of the Dr. von Hauner Children's Hospital Munich received 24h continuous ondansetron infusion at dosages of 8 mg per 24h in patients ≤15 kg BW, 16 mg per 24h in patients of >15–30 kg BW, 24 mg per 24h in patients of >30–45 kg BW, and a maximum dose of 32 mg per 24h in patients with a BW of >45 kg. Ondansetron was administered through the whole conditioning period until 24 hours after the last administration of a chemotherapeutic agent.

Dimenhydrinate (3 x 1.0 mg per kg BW per day; max. 3 x 62 mg; as a short IV infusion), metoclopramide (2 x - 5–10 mg per day; intravenously), or levomepromazine perfusor (0.1 mg per kg BW per day; max. 0.2 mg/kg per day; as 24-hour continuous infusion) were allowed as antiemetic on-demand medication.

Safety and Tolerance

Liver and kidney function were evaluated using laboratory markers as well as electrolytes that were monitored daily, starting on the day before starting the conditioning chemotherapy (Baseline) until 5 days after autoHSCT (End). Baseline values as well as minimum/maximum values (Min/Max) during the observation period and end values were analyzed and compared between the study cohorts. Normal blood levels of the parameters were defined as: alanine aminotransferase (ALT) ≤39 U/L (units per liter), aspartate aminotransferase (AST) ≤59 U/L, total bilirubin ≤1.1 mg/dL (milligram per deciliter), creatinine ≤0.7 mg/dL, urea ≤46 mg/dL, potassium 3.4–4.9 mmol/L (millimole per liter), calcium 2.0–2.6 mmol/L, and sodium 134 mmol/L - 145 mmol/L. Increases to >1.5 and >2.5-fold the normal limits (ALT, AST, total bilirubin, creatinine and urea) and decreases of potassium (<3.4 mmol/L and <3.0 mmol/L), calcium (<2.0 mmol/L and <1.8 mmol/L), and sodium (<134 mmol/L and <130 mmol/L) were compared between the two cohorts.

Clinical adverse events as defined by the United States National Cancer Institute's Common Terminology Criteria for Adverse Events were documented and analyzed.[25]

Efficacy

The efficacy of the antiemetic prophylaxis regimen was determined by the percentage of patients experiencing vomiting, the documented vomiting events, the percentage of patients receiving additional on-demand medication, the number of administered doses of on-demand medication and the phases of the observation period (0–24h, >24–120h, and >120h-240h after the first administration of a highly emetogenic agent of the conditioning chemotherapy).

Statistical Analysis

For two-sample contingency analyses, the two-tailed Fisher's exact test was used. Comparisons of the number of vomiting events or administered doses of on-demand medication between the two study cohorts (control group and fosaprepitant group) and subcohorts (ondansetron vs granisetron subgroup) were performed using the rateratio. test package of R.

Significant increases or decreases in the determined median values of the analyzed blood parameters beyond the indicated upper or lower normal limits were identified using a Wilcoxon signed-rank test. If significant increases or decreases were detected, the Wilcoxon matched-pairs signed-rank test was used for inferential statistical analyses between the baseline, and the maximum/minimum values.

Statistical tests and figures were created with GraphPad Prism for Windows, version 8.4.1 (GraphPad Software Inc., La Jolla, CA, USA), or with R (The R Foundation for Statistical Computing, Institute for Statistics and Mathematics, University of Economics and Business Vienna, Austria). *P*-values of $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***), and $p<0.0001$ (****) were defined as statistically significant and are indicated in the bar charts.

Results

Patient Characteristics

A total of 70 pediatric patients with a median age of 4.9 years (range 0.8–17.5 years; 67.1% males) who underwent autoHSCT for treatment of cerebral tumor (n=1; 1.4%)

choriocarcinoma (n=1; 1.4%), embryopnal liver sarcoma (n=1; 1.4%), ependymoblastoma (n=2; 2.9%), ependymoma (n=1; 1.4%), Ewing's sarcoma (n=8; 11.4%), germ cell tumor (n=3; 4.3%), hepatoblastoma (n=1; 1.4%), Hodgkin's lymphoma (n=3; 4.3%), medulloblastoma (n=4; 5.7%), nephroblastoma (n=2; 2.9%), nerve sheath tumor (n=1; 1.4%), neuroblastoma (n=31; 44.3%), pinealoblastoma (n=4; 5.7%), PNET (n=3; 4.3%), retinoblastoma (n=1; 1.4%), or rhabdoid tumor (n=3; 4.3%) were analyzed. Of these 70 patients, 35 (50.0%) each were analyzed in the control group (CG; median age 4.8 years, range 1.3–17.1 years) or the fosaprepitant group (FG; median age 5.1 years, range 0.8–17.5 years). The patients received a median of 4.8 x 10^6 (range 0.9–20.0 x 10^6) per kg BW autologously-derived CD34+ stem cells for autoHSCT and were discharged at a median of 30 days (range 16–67 days) after autoHSCT. The patient characteristics of both study cohorts are summarized in Table 1. No statistically significant differences in patient characteristics were detected between the two study groups (p>0.05).

Table 1 Patient Characteristics

	Control Group		Fosaprepitant Group		*p*-value
	N=35		N=35		
	n	(%)	n	(%)	
No. of patients	35	(100.0)	35	(100.0)	
Age median (range)	4.8	(1.3–17.1)	5.1	(0.8–17.5)	
Age [years]					
0.5-<2	4	(11.4)	2	(5.7)	0.6733
2–6	17	(48.6)	23	(65.7)	0.2270
7–12	9	(25.7)	5	(14.3)	0.3088
13 – <18	5	(14.3)	5	(14.3)	>0.9999
Sex					
Male	26	(74.3)	21	(60.0)	0.3088
Female	9	(25.7)	14	(40.0)	
Diagnosis					
Cerebral tumor	1	(2.9)	0	(0.0)	>0.9999
Choriocarcinoma	1	(2.9)	0	(0.0)	>0.9999
Embryonal liver sarcoma	0	(0.0)	1	(2.9)	>0.9999
Ependymoblastoma	2	(5.7)	0	(0.0)	0.4928
Ependymoma	1	(2.9)	0	(0.0)	>0.9999
Ewing's sarcoma	3	(8.6)	5	(14.3)	0.7096
Germ cell tumor	3	(8.6)	0	(0.0)	0.2391
Hepatoblastoma	0	(0.0)	1	(2.9)	>0.9999
Hodgkin's Lymphoma	2	(5.7)	1	(2.9)	>0.9999
Medulloblastoma	1	(2.9)	3	(8.6)	0.6139
Nephroblastoma	2	(5.7)	0	(0.0)	0.4928
Nerve sheath tumor	1	(2.9)	0	(0.0)	>0.9999
Neuroblastoma	13	(37.1)	18	(51.4)	0.3359
Pinealoblastoma	3	(8.6)	1	(2.9)	0.6139
PNET	0	(0.0)	3	(8.6)	0.2391
Retinoblastoma	0	(0.0)	1	(2.9)	>0.9999
Rhabdoid tumor	2	(5.7)	1	(2.9)	>0.9999

Abbreviations: n, sample size; N, total cohort size; *p*-value, probability value; PNET, primitive neuroectodermal tumor.

Conditioning Chemotherapy

A schematic overview of the administered conditioning chemotherapy regimens is displayed in Table 2. All patients received a highly emetogenic conditioning regimen as defined by the POGO classifications.[24] The median duration of the conditioning chemotherapy was 6 days (range 3–8).

Efficacy – Ondansetron vs Granisetron

In this analysis, pediatric patients of two study sites were analyzed. The two university children's hospitals used either an ondansetron or a granisetron-based antiemetic prophylaxis regimen. Patients of both study sites were analyzed in either the control or the fosaprepitant group. Both cohorts were then subdivided into an ondansetron and a granisetron subgroup in order to identify a difference in the antiemetic efficacy of ondansetron and granisetron. Efficacy data of the ondansetron and granisetron subgroups of each patient cohort were compared (Supplementary Table ST1).

In the control group, 19 of 35 patients (54.3%) received ondansetron only (ondansetron subgroup), while the other 16 patients (45.7%) received granisetron only (granisetron subgroup). In the ondansetron subgroup a median of 5 vomiting events (range 1–17) per patient occurred during the whole observation period (0–240h after starting the conditioning chemotherapy), which was not significantly different (p>0.9999) compared with the granisetron subgroup patients, who experienced a median of 4 vomiting events (range 1–19) per patient. Likewise, the total number of vomiting events registered during the whole observation period was not significantly different between the two subgroups (248 vs 219 vomiting events; p=0.6407).

Analyzing the use of antiemetic on-demand medication, a significant difference was only detected for the total number of administered doses of dimenhydrinate (ondansetron subgroup: 249 doses vs granisetron subgroup: 84 doses; p<0.0001).

In the fosaprepitant group, 10 of 35 patients (28.6%) received ondansetron only (ondansetron subgroup), while

Table 2 Conditioning Chemotherapy

ID	Name	Dosage	Emetogenic Potential (POGO Guidelines)	Control Group		Fosaprepitant Group	
				N=35		N=35	
				n	(%)	n	(%)
A1	Bu/Mel	Busulfan 4 x 4 mg/kg Melphalan 1 x 140 mg/m^2	4	4	(11.4)	7	(20.0)
A2	Bu/Mel	Busulfan 4 x 4 mg/kg Melphalan 2 x 70 mg/m^2	4			2	(5.7)
A3	Bu/Mel	Busulfan 4 x 4.8 mg/kg Melphalan 1 x 140 mg/m^2	4			2	(5.7)
B1	Carbo/Eto	Carboplatin 4 x 500 mg/m^2 Etoposide 4 x 250 mg/m^2	4	4	(11.4)	1	(2.9)
B2	Carbo/Eto	Carboplatin 3 x 500 mg/m^2 Etoposide 4 x 500 mg/m^2	4	1	(2.9)		
B3	Carbo/Eto	Carboplatin 4 x 500 mg/m^2 Etoposide 4 x 500 mg/m^2	4	1	(2.9)		
B4	Carbo/Eto	Carboplatin 3 x 500 mg/m^2 Etoposide 1 x 250 mg/m^2	4			1	(2.9)
B5	Carbo/Eto	Carboplatin 4 x 500 mg/m^2 Etoposide 4 x 125 mg/m^2	4			1	(2.9)
B6	Carbo/Eto	Carboplatin 4 x 375 mg/m^2 Etoposide 4 x 250 mg/m^2	4			1	(2.9)
C1	Carbo/Eto/Ifosf.	Carboplatin 5 x 120 mg/m^2 Etoposide 5 x 300 mg/m^2 Ifosfamide 5 x 2000 mg/m^2	4	1	(2.9)		
C2	Carbo/Eto/Ifosf.	Carboplatin 4 x 120 mg/m^2 Etoposide 5 x 300 mg/m^2 Ifosfamide 4 x 2500 mg/m^2	4	1	(2.9)		
D1	Carbo/Eto/TT	Carboplatin 4 x 500 mg/m^2 Etoposide 4 x 250 mg/m^2 Thiotepa 4 x 150 mg/m^2	4	1	(2.9)	2	(5.7)
D2	Carbo/Eto/TT	Carboplatin 4 x 500 mg/m^2 Etoposide 4 x 500 mg/m^2 Thiotepa 4 x150 mg/m^2	4	1	(2.9)		
D3	Carbo/Eto/TT	Carboplatin 3 x 500 mg/m^2 Etoposide 3 x 250 mg/m^2 Thiotepa 4 x150 mg/m^2	4	1	(2.9)		
E1	Carbo/TT	Carboplatin 3 x 500 mg/m^2 Thiotepa 3 x 500 mg/m^2	4	1	(2.9)		
E2	Carbo/TT	Carboplatin 2 x 500 mg/m^2 Thiotepa 3 x 300 mg/m^2	4	1	(2.9)		

(*Continued*)

Table 2 (Continued).

ID	Name	Dosage	Emetogenic Potential (POGO Guidelines)	Control Group		Fosaprepitant Group	
				N=35		N=35	
				n	(%)	n	(%)
E3	Carbo/TT	Carboplatin 3 x 350 mg/m^2 Thiotepa 3 x 200 mg/m^2	4			1	(2.9)
E4	Carbo/TT	Carboplatin 4 x 500 mg/m^2 Thiotepa 3 x 300 mg/m^2	4			1	(2.9)
F1	Cy/TT	Cyclophosphamide 1 x 1500 mg/m^2 Thiotepa 3 x 300 mg/m^2	4	1	(2.9)		
F2	Cy/TT	Cyclophosphamide 3 x 1500 mg/m^2 Thiotepa 3 x 300 mg/m^2	4			2	(5.7)
G1	Cyt/Mel/Eto/Carm	Cytarabine 4 x 200 mg/m^2 Melphalan 1 x 140 mg/m^2 Etoposide 4 x 200 mg/m^2 Carmustin 1 x 300 mg/m^2	4	1	(2.9)		
G2	Cyt/Mel/Eto/Carm	Cytarabine 1 x 1600 mg/m^2 Melphalan 1 x 140 mg/m^2 Etoposide 4 x 200 mg/m^2 Carmustin 1 x 300 mg/m^2	4			1	(2.9)
H	Mel/Carbo	Melphalan 1 x 45 mg/m^2 Carboplatin 3 x 500 mg/m^2	4			1	(2.9)
I1	Mel/Carbo/Eto	Melphalan 4 x 45 mg/m^2 Carboplatin 3 x 500 mg/m^2 Etoposide 1 x 40 mg/kg	4	8	(22.9)	3	(8.6)
I2	Mel/Carbo/Eto	Melphalan 3 x 60 mg/m^2 Carboplatin 4 x 300 mg/m^2 Etoposide 4 x 200 mg/m^2	4	2	(5.7)		
I3	Mel/Carbo/Eto	Melphalan 4 x 45 mg/m^2 Carboplatin 2 x 300 mg/m^2 Etoposide 1 x 40 mg/kg	4	1	(2.9)		
I4	Mel/Carbo/Eto	Melphalan 4 x 45 mg/m^2 Carboplatin 3 x 400 mg/m^2 Etoposide 1 x 800 mg/m^2	4	1	(2.9)		
I5	Mel/Carbo/Eto	Melphalan 2 x 45 mg/m^2 Carboplatin 3 x 250 mg/m^2 Etoposide 1 x 20 mg/kg	4			2	(5.7)
J	Mel/Eto	Melphalan 1 x 140 mg/m^2 Etoposide 4 x 200 mg/m^2	4	1	(2.9)		
K1	Treo/Mel	Treosulfan 3 x 12 g/m^2 Melphalan 1 x 140 mg/m^2	4	2	(5.7)	5	(14.3)

(*Continued*)

Table 2 (Continued).

ID	Name	Dosage	Emetogenic Potential (POGO Guidelines)	Control Group		Fosaprepitant Group	
				N=35		N=35	
				n	(%)	n	(%)
K2	Treo/Mel	Treosulfan 3 x 12 g/m^2 Melphalan 1 x 70 mg/m^2	4			1	(2.9)
K3	Treo/Mel	Treosulfan 2 x 12 g/m^2 Melphalan 1 x 140 mg/m^2	4			1	(2.9)
L	Eto/Cis/Ifosf	Etoposide 5 x 300 mg/m^2 Cisplatin 5 x 20 mg/m^2 Ifosfamide 5 x 2000 mg/m^2	4	1	(2.9)		

Notes: The table shows a systematic overview of the administered conditioning chemotherapy prior to autologous hematopoietic stem cell transplantation. All regimens used were highly emetogenic (emetogenic potential grade 4) according to the POGO classifications.[24]
Abbreviations: n, sample size; N, total cohort size.

the other 25 patients (71.4%) received granisetron only (granisetron subgroup). In the ondansetron subgroup a median of 6 vomiting events (range 1–12) per patient occurred during the whole observation period (0–240h), which was significantly higher ($p<0.05$) compared with the results of the granisetron subgroup patients, who experienced a median of 2 vomiting events (range 1–8) per patient. Likewise, the total number of vomiting events registered during the whole observation period was significantly higher in the granisetron subgroup (ondansetron: 86 events vs granisetron: 119 events; $p<0.0001$).

Analyzing the use of antiemetic on-demand medication in the fosaprepitant group, a significant difference was detected for the total number of administered doses of dimenhydrinate (ondansetron subgroup: 104 doses vs granisetron subgroup: 39 doses; $p<0.0001$) and metoclopramide (ondansetron subgroup: 0 doses vs granisetron subgroup: 23 doses; $p<0.0001$).

Efficacy – Control Group vs Fosaprepitant Group

In the first time period (0–24h), patients of the control and the fosaprepitant group experienced a median of 2 (range 1–8) and 1 (range 1–3) vomiting events per patient, respectively ($p>0.9999$). The percentage of patients who experienced vomiting in this time period was not significantly different between the two groups (control group: 71.4% vs fosaprepitant group: 51.4%; $p=0.1401$), although significantly more ($p<0.01$) vomiting events were registered in the control group (64 vs 22 events) (Figure 1).

In the second time period (>24h-120h), patients of the control and the fosaprepitant group experienced a median of 3 (range 1–12) and 2 (range 1–11) vomiting events per patient, respectively ($p>0.9999$). The percentage of patients who experienced vomiting in this time period was significantly higher in the control group (control group: 100% vs fosaprepitant group: 74.3%; $p<0.01$). Likewise, significantly more ($p<0.0001$) vomiting events were registered in the control group (135 vs 78 events) (Figure 1).

In the third time period (>120h-240h), patients of the control and the fosaprepitant group experienced a median of 4 (range 1–19) and 2 (range 1–12) vomiting events per patient, respectively ($p=0.6875$). The percentage of patients who experienced vomiting in this time period did not significantly differ between the two groups (control group: 94.3% vs fosaprepitant group: 80.0%; $p=0.3438$), although significantly more ($p<0.0001$) vomiting events were registered in the control group (268 vs 105 events) (Figure 1).

Analyzing the whole observation period (0–240h), significantly ($p<0.0001$) more vomiting events were registered in the control group (467 events) compared with the fosaprepitant group (205 events), and significantly more patients ($p<0.01$) of the control group experienced vomiting in all three time periods (control group: 68.6% vs fosaprepitant group: 28.6%) (Figure 1).

Among all 70 analyzed children, the complete absence of vomiting in all three time periods was only achieved in one child (1.4%), who received an antiemetic prophylaxis with fosaprepitant and granisetron.

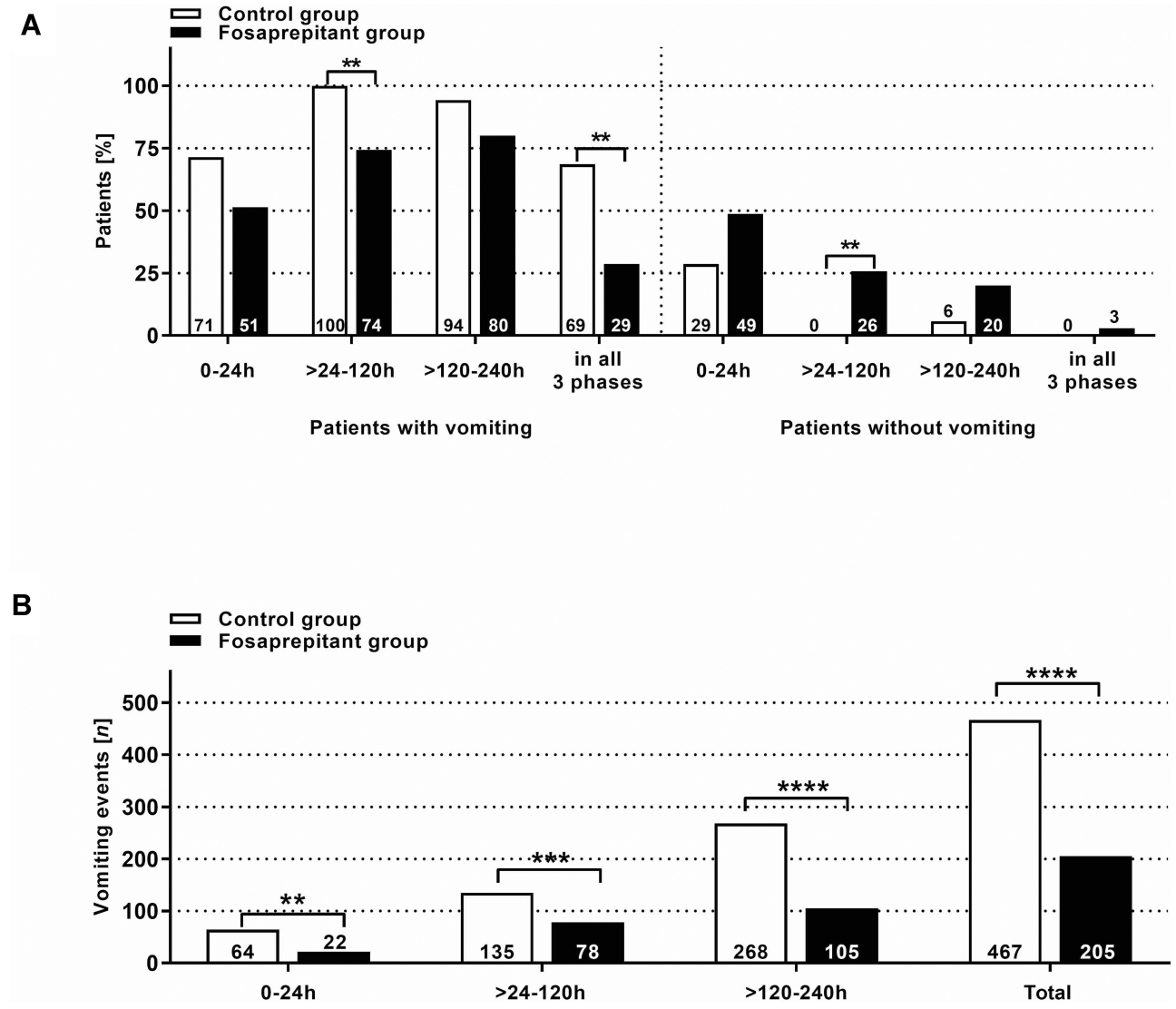

Figure 1 Efficacy of antiemetic prophylaxis. The graph displays the efficacy of the administered antiemetic prophylaxis either with ondansetron/granisetron only (control group) or ondansetron/granisetron in combination with fosaprepitant (fosaprepitant group). (**A**) shows the percentage of patients of both study cohorts who did or did not experience vomiting during three analyzed time periods (0–24h, >24–120h, or >120–240h) or the whole observation period ("in all 3 phases"; 0–240h) after the first administration of a highly emetogenic chemotherapeutic agent of the conditioning chemotherapy prior to autoHSCT. (**B**) displays the registered vomiting events during these three phases and the cumulative events in both groups. Symbols indicate **p<0.01| ***p<0.001 | ****p<0.0001.

Efficacy – On-Demand Antiemetic Medication

The median number of administered doses of dimenhydrinate per patient did not significantly differ between the two groups (control group: median 9 (range 2–24) vs fosaprepitant group: 2 doses (range 1–36); p=0.0654). Although the percentage of patients who received dimenhydrinate did not significantly differ (control group: 97.1% vs fosaprepitant group: 74.3%; p=0.0914), the total number of administered doses was significantly higher in the control group (333 doses vs 143 doses; p<0.0001) (Figure 2).

Metoclopramide was administered a median of 3 times (range 2–6 doses) per patient in 4 (11.4%) patients and at median 6 times (range 4–8; p=0.5078) per patient in 4 patients (11.4%; p>0.9999) of the control group and the fosaprepitant group, respectively. The total number of administered doses of metoclopramide did not significantly differ between the two groups (control group: 14 doses vs fosaprepitant group: 23 doses; p=0.1877).

In both study groups, 3 (8.6%) of the patients received levomepromazine per 24-hour intravenous infusion. In the control group, the three patients received the levomepromazine perfusor at median over 5 days (range 4–8), while

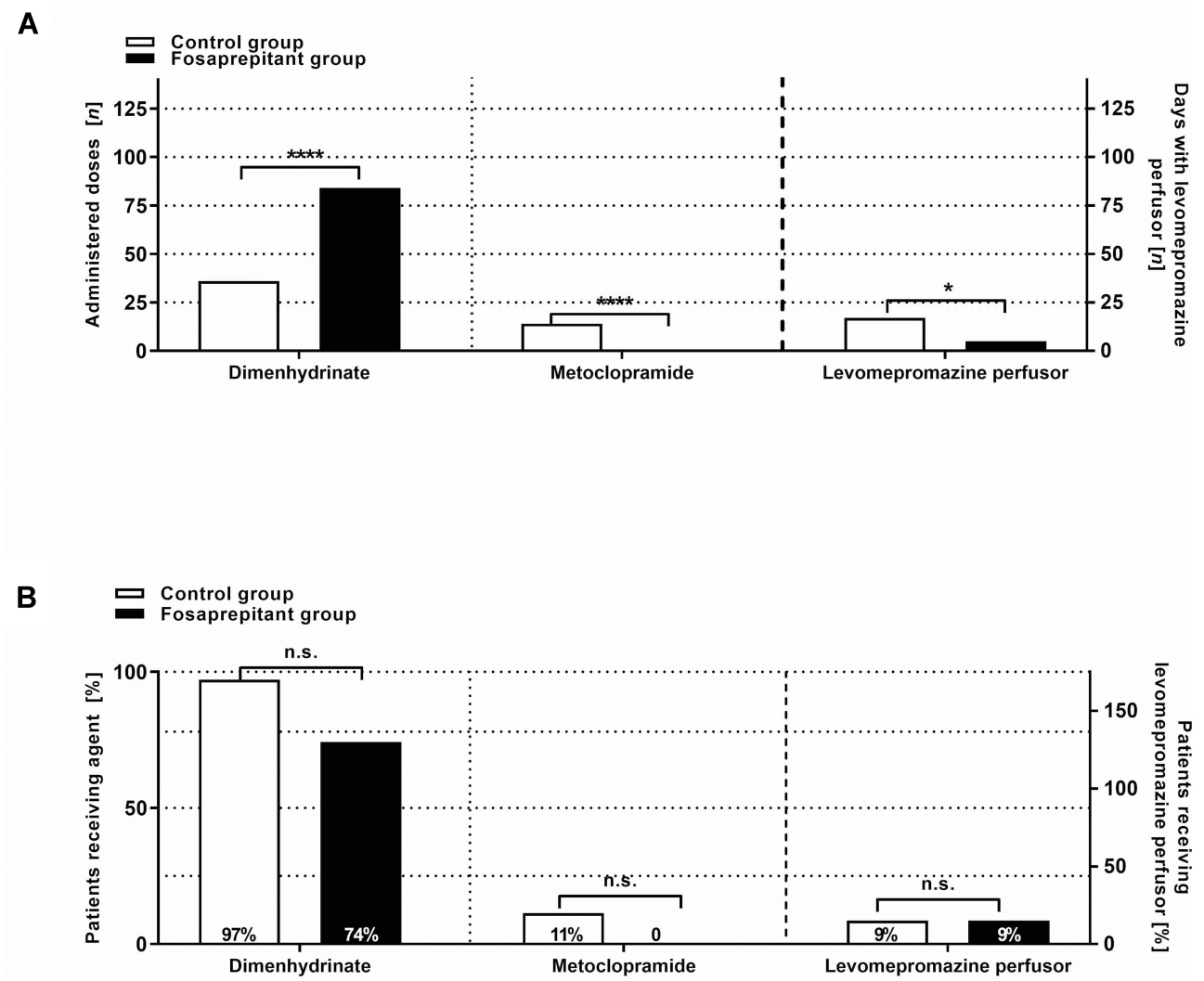

Figure 2 On-demand antiemetic medication. The graph shows the total number of administered doses (**A**) or the percentage of patients (**B**) receiving on-demand medication with dimenhydrinate, metoclopramide, or levomepromazine per 24-hour intravenous infusion during the conditioning chemotherapy prior to autoHSCT. Although the percentage of patients receiving dimenhydrinate (p=0.0914), metoclopramide (p=0.1142) or levomepromazine per 24-hour intravenous infusion (p>0.9999) did not significantly differ between the two groups, significantly more doses of dimenhydrinate (p<0.0001) and levomepromazine (p<0.05) were administered in the control group. Symbols indicate *p<0.05 | ****p<0.0001.

the three fosaprepitant group patients received it at median for 2 days (range 1–2 days; p=0.4531).

Safety and Tolerance

Discontinuation of the antiemetic prophylaxis was not indicated for any of the patients of the two study groups. In the control group, 2 patients (5.7%) died during the first 200 days after autoHSCT. Reasons for death were relapse of the underlying disease (n=1; 50%), or RSV pneumonia (n=1, 50%). In the fosaprepitant group, 3 of the patients (8.6%) died within the first 200 days after autoHSCT, either after progress (n=1; 33.3%) or relapse (n=2; 66.6%) of the underlying disease.

Statistically significant increases or decreases of the median hepatic or renal parameters and electrolytes were not detected in either study cohorts (p>0.05; Supplementary Figure SF1). Isolated increases of the analyzed blood parameters beyond 1.5- or 2.5-fold the normal upper limits or clinically significant decreases below the lower limits (potassium, calcium, sodium) were registered and compared between the two groups (Table 3). Statistically significant differences could not be detected (p>0.05), except for sodium: significantly more patients of the control group experienced decreases of sodium <134 mmol/L compared with the fosaprepitant group (42.9% vs 11.4% of the patients; p<0.01). Clinical adverse events were low in number and did not significantly differ (p>0.05) between the two study groups (Table 3).

Table 3 Liver and Kidney Parameters and Clinical Adverse Events

Laboratory Markers	Control Group		Fosaprepitant Group		*p*-value
	N=35		N=35		
	n	(%)	n	(%)	
Increase ALT | normal value: ≤39 U/L					
≥1.5 x normal value (≥58.5 U/L)	6	(17.1)	1	(2.9)	0.1060
≥2.5 x normal value (≥97.5 U/L)	6	(17.1)	5	(14.3)	>0.9999
Increase AST | normal value: ≤59 U/L					
≥1.5 x normal value (≥88.5 U/L)	2	(5.7)	2	(5.7)	>0.9999
≥2.5 x normal Value (≥147.5 U/L)	4	(11.4)	2	(5.7)	0.6733
Increase total bilirubin | normal value: ≤1.1 mg/dL					
≥1.5 x normal value (≥1.65 mg/dL)	0	(0.0)	0	(0.0)	>0.9999
≥2.5 x normal value (≥2.75 mg/dL)	0	(0.0)	0	(0.0)	>0.9999
Increase creatinine | normal value: ≤0.7mg/dL					
≥1.5 x normal value (≥1.05 mg/dL)	0	(0.0)	0	(0.0)	>0.9999
≥2.5 x normal value (≥1.75 mg/dL)	0	(0.0)	0	(0.0)	>0.9999
Increase urea | normal value: ≤46mg/dL					
≥1.5 x normal value (≥69 mg/dL)	0	(0.0)	0	(0.0)	>0.9999
≥2.5 x normal value (≥115 mg/dL)	0	(0.0)	0	(0.0)	>0.9999
Decrease potassium | normal value: 3.4–4.9 mmol/L					
<3.4 mmol/L	3	(8.6)	1	(2.9)	0.6139
<3.0 mmol/L	2	(5.7)	0	(0.0)	0.4928
Decrease calcium | normal value: 2.0–2.6 mmol/L					
<2.0 mmol/L	2	(5.7)	4	(11.4)	0.6733
<1.8 mmol/L	0	(0.0)	0	(0.0)	>0.9999
Decrease sodium | normal value: 134−145 mmol/L					
<134 mmol/L	15	(42.9)	4	(11.4)	0.0063
<130 mmol/L	1	(2.9)	0	(0.0)	>0.9999
Clinical adverse events					
Exanthema	0	(0.0)	1	(2.9)	>0.9999
Urticaria	1	(2.9)	0	(0.0)	>0.9999
Dizziness	0	(0.0)	1	(2.9)	>0.9999
Headache	0	(0.0)	1	(2.9)	>0.9999
Fever	1	(2.9)	2	(5.7)	>0.9999
Diarrhea	3	(8.6)	1	(2.9)	0.6139
Edema of the tongue	0	(0.0)	1	(2.9)	>0.9999

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; mg/dL; milligram per deciliter; mmol/L; millimole per liter; n, sample size; N, total cohort size; *p*, probability value; U/L, units per liter.

Fosaprepitant is a known inhibitor of the CYP3A4 and CYP2C9 and therefore it potentially influences the efficacy and toxicity of other substrates of these enzymes, such as cyclophosphamide.[26] In the fosaprepitant group, two patients received a conditioning chemotherapy with cyclophosphamide. Blood levels of cyclophosphamide were not monitored in these two patients.

Discussion

Chemotherapy-induced nausea and vomiting is a highly distressing side effect of emetogenic chemotherapy and it is difficult to control, particularly in pediatric patients undergoing myeloablative conditioning chemotherapy for HSCT. Complete control of CINV is poorly achieved in these patients despite extensive research and development

of comprehensive multi-drug antiemetic prophylaxis regimens in recent years.[10,14,22]

To date, study data on the use of the NK_1-receptor antagonist fosaprepitant in patients undergoing autologous HSCT is scarce and analyzed for adult patients only.[20,21,27] In children receiving highly emetogenic chemotherapy, fosaprepitant was effective and well tolerated.[17,18,23,28–31]

In our previously performed analysis, it was demonstrated that the addition of single-dose IV fosaprepitant directly before starting the moderately or highly emetogenic conditioning chemotherapy prior to allogeneic HSCT, was safe and superior to the standard antiemetic prophylaxis regimen.[18] This is the first comparative analysis regarding the use of a fosaprepitant-based antiemetic prophylaxis regimen during highly emetogenic conditioning chemotherapy prior to autoHSCT in pediatric patients with hemato-oncological malignancies.

Limitations of this analysis are its study design. However, given the limited data accessibility and the use in pediatric patients, a randomized study design and use of a placebo are considered unethical at this point.

It was demonstrated that the safety and toxicity of the administered antiemetic prophylaxis regimens with or without fosaprepitant were similar. Clinical adverse events and clinically-relevant increases of renal or hepatic blood markers and decreases of electrolytes occurred marginally in both study cohorts. Other side effects or adverse events that could potentially be ascribed to fosaprepitant did not arise. None of the patients was withdrawn from the antiemetic prophylaxis. It was therefore concluded that fosaprepitant was well tolerated in these patients.

The results of the comparison of the antiemetic efficacy of the two administered 5-HT_3-antagonists granisetron and ondansetron do not allow a clear statement, since the results were inconsistent. Prospective randomized trials in pediatric and adult patients undergoing autologous or allogeneic HSCT did not detect statistically significant difference between the antiemetic efficacy of granisetron and ondansetron.[32–34]

Although the efficacy analysis of the control and the fosaprepitant group showed that the percentage of pediatric patients experiencing vomiting was only lower in the second time period >24–120h (100% vs 74.3%), a clear benefit of the addition of fosaprepitant was demonstrated: besides the significant reduction of vomiting events in all three analyzed time periods (0–24h: 2.9-fold reduction | >24–120h: 1.7-fold reduction | >120–240h: 2.6-fold reduction | 0–240h: 2.3-fold reduction), the use of antiemetic on-demand medication with dimenhydrinate (333 vs 143 doses), and levomepromazine perfusor (17 vs 5 days use of perfusor) was reduced.

Nausea is a relevant factor of CINV and can be assessed specifically in children using the Pediatric Nausea Assessment Tool (PeNAT), which is validated for pediatric patients between 4 and 17 years of age.[35] Given the study design and the comparison with a control cohort, the efficacy analysis was based entirely on the documented vomiting events, rather than the occurrence of nausea. Complete control rates were higher in our previous study: from 32 pediatric patients undergoing highly emetogenic conditioning chemotherapy for allogeneic HSCT and receiving granisetron and fosaprepitant at the same dosages, 34.4% were free of vomiting in the first 240h after starting the chemotherapy, and 15.6% achieved a complete control (free of vomiting without the use of on-demand antiemetics).[18]

AutoHSCT is a rather rarely performed procedure.[9] Despite the relatively small patient cohorts analyzed in this work, its results show the beneficial antiemetic effects of the fosaprepitant-based regimen and reaffirm the findings of previous analyses of fosaprepitant in children during moderately and highly emetogenic chemotherapy.[17,23,28,30,31] In view of the unsatisfactory control rates of vomiting despite the use of fosaprepitant in the patients undergoing autoHSCT, new or different antiemetic prophylaxis regimens are urgently needed to improve the supportive care of this rare patient cohort.

Conclusions

The antiemetic prophylaxis comprising fosaprepitant single-dose intravenous infusion in addition to a 5-HT_3-antagonist (ondansetron or granisetron) was safe and more effective compared with the standard regimen with a 5-HT_3-antagonist only in pediatric patients undergoing a highly emetogenic conditioning chemotherapy prior to autologous HSCT. Fosaprepitant in combination with 5-HT_3-antagonist significantly reduced the vomiting events and the percentage of patients experiencing vomiting during the first 24h, >24–120h, and >120–240h after starting the highly emetogenic chemotherapy. The present data form the basis for larger prospective and randomized trials to substantiate these findings.

Abbreviations

µg per kg BW, microgram per kilogram bodyweight; 5-HT3, 5-hydroxytryptamine 3/serotonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase;

autoHSCT, autologous hematopoietic stem cell transplantation; BW, bodyweight; CG, control group; CINV, chemotherapy-induced nausea and vomiting; FG, fosaprepitant group; h, hour(s); HSCT, hematopoietic stem cell transplantation; i.e., id est/that is to say; IV, intravenous; kg, kilogram; maximum, max; Mb., Morbus; mg, milligram; mg/dL, milligram per deciliter; minimum, min; mmol/L, millimole per liter; n, sample size; N, study cohort size; ns, not significant; NK1, neurokinin-1; *p*, probability value; PNET, primitive neuroectodermal tumors; POGO, Pediatric Oncology Group of Ontario; U/L, units per liter.

Compliance with Ethical Standards

This analysis was performed in accordance with the Helsinki declaration adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. An ethics vote for the retrospective analysis was granted by the Ethics Committees of the University of Tübingen (775/2018BO2) and the Ludwig-Maximilian-University Munich (18-764). Formal consent is not required for this type of study. Baseline demographics, clinical factors and survival rates were abstracted from clinical and research records and maintained on a prospective basis. The legal basis for the data processing are Art. 6, 7, 9, 89 of the general data protection regulation (EU) 2016/679 of the EU in combination with §§ 4, 5, 6, 8, 9, 12, 13 of the Landesdatenschutzgesetzes Baden-Württemberg in its current form of May 25th, 2018.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflicts of interest.

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