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Impact of Palifermin on Transplant Outcomes in Children and Adolescents Undergoing Allogeneic Hematopoietic Cell Transplantation

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Abstract. *Background: Oral mucositis (OM) is considered to be one of the worst and most debilitating complications of conditioning for hematopoietic cell transplantation (HCT). Prevention and treatment of this complication is one of the utmost priorities of supportive therapy during transplant procedure. The objective of this study was the analysis of the influence of palifermin, keratinocyte growth factor (KGF), on transplant outcomes in patients undergoing allo-HCT. Patients and Methods: A total of 253 allo-HCTs performed between 2003-2018 in patients aged 0-19 years at a single center were analyzed. KGF was administered in 161 HCTs. Uni- and multivariate risk factor analyses were performed. Results: In spite of reducing the duration and grade of mucositis, no prognostic impact of KGF was shown for overall survival, event-free survival, relapse incidence, acute and chronic graft-versus-host disease (GVHD), nor GVHD-free relapse-free survival. Conclusion: Palifermin had no impact on transplant outcomes in children and adolescents undergoing allo-HCT.*

Oral mucositis (OM) is one of the most common and distressful (debilitating) complications in cancer chemotherapy, radiotherapy, conditioning and transplantation (1-5). It is often accompanied by pain, dysgeusia, odynophagia and occurs more frequent in children and adolescents than that in adult patients (2). OM is reported in 75% to 100% patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) (6-10).

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Numerous methods for the prevention and treatment of OM have been developed including palifermin [recombinant human keratinocyte growth factor (KGF)], granulocyte-colony stimulating factor, amifostine, aloe vera, honey and polymixin/tobramycin/amphotericin, antibiotic pastille/paste, intravenous glutamine, polaprezinc sodium alginate suspension and sucralfate, cryotherapy, and laser (2, 11). Current recommendations of Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology for the prevention of OM include: KGF, benzydamine, morphine, cryotherapy and low-level laser light therapy (12, 13).

The use of palifermin in prophylaxis can significantly reduce the incidence and severity of mucositis in patients after total body irradiation (TBI)/high-dose chemotherapy. We previously showed that patients receiving KGF after autologous HCT had better overall survival (OS) (5). We have also shown that patients with allo-HCT who received palifermin prophylactically, had shorter duration of mucositis (median: 9 *vs*. 13 days), lower OM grade (median: III *vs*. IV), shorter total parenteral nutrition (median: 19 *vs*. 22 days) and lower incidence of episodes of febrile neutropenia (median: 39% *vs*. 83%) (14). Since data on the effect of palifermin on outcomes of allo-HCT in children are scarce, we analyzed the impact of prophylactic use of palifermin on transplant outcomes in a large cohort of children undergoing allo-HCT.

Patients and Methods

Study design. We carried out analysis of the impact of palifermin administered under compassionate use on short-term transplant outcomes in comparison to group of patients with HCT who were not treated with palifermin.

Patients. Overall 253 allo-HCTs performed between 2003-2018 in patients aged 0-19 years (92 female; 161 male) at a single center were analyzed. The indication for allo-HCT were acute lymphoblastic

leukemia in 107 (42.3%), acute myelogenous leukemia in 60 (23.7%), severe aplastic anemia in 35 (13.8%), primary immunodeficiency in 16 (6.3%), acute biphenotypic leukemia in eight (3.2%), myelodysplastic syndrome in six (2.3%), Hodgkin's lymphoma in six (2.3%), chronic myelogenous leukemia in five (1.9%), juvenile myelo-monocytic leukemia in three (1.1%) and other indications in seven (2.8%). In 162 (64.0%) cases, the donor was matched unrelated (MUD), in 78 (30.9%) matched family donor (MFD), mismatched unrelated donor in seven (2.8%) and haploidentical donor in six (2.3%). In 60.9% (154/253) of HCTs, patients were in the first complete remission (CR1), while others were in the second or subsequent remission (CR>1). In 69.2% (175/253), a myeloablative conditioning regimen was used, and in 30.8% (78/253) reduced intensity regimen/reduced toxicity conditioning was used.

Grading of mucositis. The intensity of OM was assessed according to the World Health Organization scale, determining grade 0 as having no symptoms; grade I with soreness and erythema; grade II with erythema and ulcers, and ability to swallow a solid diet; grade III with ulcers and extensive erythema, inability to a swallow solid diet; grade IV with mucositis to the extent that alimentation is not possible (15).

KGF administration. A total of six doses of KGF as palifermin (Kepivance; Biovitrum, Stockholm, Sweden) was administered intravenously at the dose of 60 μg/kg/day once daily for 3 consecutive days before the start of the conditioning treatment (chemotherapy or radiotherapy) and for 3 consecutive days after the transplantation starting from day +1. Between the third dose and the beginning of conditioning, as well as between the end of graft infusion and the fourth dose of palifermin, an interval of 24 hours was kept. Uniform, standard anti-infective prophylaxis was applied for all patients undergoing allo-HCT (14, 16).

Definitions. Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil counts $>0.5\times10^6$/l. Platelet engraftment was defined as the first of 3 consecutive days with platelets $>20\times10^6$/l without platelet transfusions during the previous 7 days. Severe graft-*versus*-host disease (GVHD) was defined as grade III-IV acute (aGVHD) and chronic (cGVHD).

Bioethical issues. Informed consent for each patient before the allo-HCT procedure was provided, as well for data analysis, and publication. The work described in this article was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals. The study was approved by Collegium Medicum in Bydgoszcz Bioethical Committee No. 591/2018.

Statistical analysis. Non-categorical variables were compared by the Mann–Whitney test, and categorical variables by the chi-squared test, with odds ratio (OR) and 95% confidence interval (95% CI). The primary endpoint of the study was OS, while secondary event-free survival (EFS), relapse incidence (RI), incidence of GVHD, and severe GVHD-free relapse-free survival (GRFS). The survival curves were determined by the Kaplan–Meier method and compared with the log-rank test. Risk factor analysis was performed in a univariate Cox model. Factors significant were analyzed in multivariate Cox models. The results of the multivariate analysis are presented as hazard ratios (HR) with their 95% CIs. The following data were included in the risk factor analysis: Age, primary diagnosis and its stage, source of hematopoietic cells, type of transplant, conditioning, day of neutrophil recovery, presence of acute and chronic GVHD, total parenteral nutrition, and evidence of grade 3/4 OM. A relic of $p<0.05$ was considered statistically significant. The analysis was performed using the statistical package SPSS 25.0 (IBM, Armonk, NY, USA).

Results

Palifermin was administered to 161 patients with allo-HCT, and another 92 with HCTs were regarded as the control group. Patients characteristic are presented in Table I. There were no differences in baseline data between groups, except for a higher rate of MUD-HCTs in the palifermin-treated group (107 *vs*. 45; *i.e*. 66.5% *vs*. 48.9%, respectively; $p=0.009$), and higher rate of use of anti-thymocyte globulin, routinely administered in MUD-HCTs. Patients who received palifermin in prophylaxis had comparable 1-year OS to others (0.75 *vs*. 0.66, $p=0.244$), EFS (0.69 *vs*. 0.64, $p=0.288$), RI (0.19 *vs*. 0.17, $p=0.503$) and GRFS (0.57 *vs*. 0.57, $p=0.477$) (Figure 1).

Overall survival. In univariate analysis, the following factors were found to have positive prognostic factors: Karnofsky/Lansky score ≥90 (HR=0.27, 95% CI=0.15-0.49; $p<0.001$), neutrophil recovery (HR=0.09, 95% CI=0.05-0.21; $p<0.001$), platelet recovery (HR=0.10, 95% CI=0.06-0.17; $p<0.001$), use of myeloablative conditioning regimen (HR=0.61, 95% CI=0.40-0.94; $p=0.026$), male gender (HR=0.81, 95% CI=0.62-0.99; $p=0.046$) and transplantation from MFD (HR=0.59, 95% CI=0.63-0.97; $p=0.038$). Transplantation in CR>1 status had an adverse prognostic impact (HR=2.12, 95% CI=1.38-3.23; $p<0.001$). The use of palifermin had no prognostic value.

Event-free survival. In univariate analysis, the following factors had prognostic value: Karnofsky/Lansky score ≥90 (HR=0.35, 95% CI=0.19-0.60; $p<0.001$), neutrophil recovery (HR=0.10, 95% CI=0.05-0.22; $p<0.001$), platelet recovery (HR=0.12, 95% CI=0.07-0.12; $p<0.001$) and age <10 years (HR=0.63, 95% CI=0.42-0.94; $p=0.023$). CR>1 status (HR=2.22, 95% CI=1.49-3.23; $p<0.001$) and solid tumor diagnosis (HR=3.70, 35% CI=1.17-12.5; $p=0.026$) were negative prognostic factors for EFS. The use of palifermin, gender, donor type, GVHD and conditioning regimen (myeloablative conditioning regimen/reduced intensity regimen) had no prognostic value.

Relapse incidence. The prognostic factors for increased RI in a univariate analysis were diagnosis of solid tumor (HR=9.09, 95% CI=2.70-33.3; $p<0.001$) and CR>1 status (HR=4.00, 95% CI=2.27-7.14; $p<0.001$). The use of palifermin had no prognostic value.

Table I. *Patient characteristics stratified by keratinocyte growth factor (palifermin) administration.*

Characteristic		With KGF		Without KGF		*p*-Value
		n	Value	n	Value	
Gender, n	Male:female	161	102:59	92	59:33	0.901
Age, years	Median (range)	161	10.7 (0.4-22.3)	92	9.9 (0.6-20.9)	0.147
Hospitalization after HCT, days	Median (range)	161	30 (8-91)	92	30 (4-79)	0.501
Year of HCT	Median (range)	161	2012 (2006-2016)	92	2017 (2003-2018)	0.001
Matched donor, n (%)	MFD + MUD	161	151 (93.8%)	92	90 (97.8%)	0.147
Matched unrelated donor, n (%)	MUD	161	107 (66.5%)	92	45 (48.9%)	0.009
Matched family donor, n (%)	MFD	161	44 (27.3%)	92	35 (38%)	0.077
Weight, kg	Median (range)	161	34 (5.0-93)	89	34 (6.6-85)	0.315
Height, cm	Median (range)	161	138 (58-188)	85	138 (66-184)	0.404
Karnofsky/Lansky score	Median (range)	161	100 (50-100)	92	100 (30-100)	0.063
Stage of disease, n (%)	CR>1	161	66 (41.0%)	92	33 (35.9%)	0.423
Hematopoietic cell source, n (%)	PB	161	101 (62.7%)	92	59 (64.1%)	0.744
Conditioning, n (%)	RIC/RTC	161	50 (31.0%)	92	29 (31.5%)	0.939
	MAC	161	111 (68.9%)	92	63 (68.5%)	0.939
	TBI	161	33 (20.5%)	92	18 (20.0%)	0.925
	ATG use	161	115 (71.4%)	92	21 (23.3%)	<0.001
	Busulfan use	161	80 (49.7%)	92	39 (43.3%)	0.334
	Treosulfan use	161	12 (7.5%)	92	9 (9.8%)	0.486
Recipient status, n (%)	CMV IgG	161	126 (78.3%)	92	72 (78.3%)	0.925
	EBV IgG	161	145 (90.1%)	92	83 (90.2%)	0.927
Donor, n (%)	CMV IgG	161	81 (50.9%)	92	48 (52.2%)	0.775
	EBV IgG	161	114 (70.8%)	92	62 (67.4%)	0.569
Dose MNC, 108/kg	Median (range)	161	8.65 (0.41-53)	92	10.27 (0.34-35.3)	0.289
Dose CD34, 106/kg	Median (range)	160	6.41 (0.8-28.3)	92	6.66 (0.49-25.2)	0.334
Time to ANC>0.5×106/l, days	Median (range)	155	18 (11-34)	73	17 (10-27)	0.229
Time to PLT>20×106/l, days	Median (range)	140	16 (0-65)	65	14 (8-55)	0.136
Time to reticulocytes >5‰, days	Median (range)	149	15 (9-43)	71	15 (12-40)	0.788
Severe GVHD, n (%)	aGVHD 3/4 or extensive cGVHD	160	25 (15.6%)	90	15 (16.7%)	0.830
Onset of severe GVHD, days	Median (range)	25	102 (15-160)	15	40 (20-120)	0.128
aGVHD grade 1-4, n (%)	Frequency	161	25 (15.5%)	92	15 (16.3%)	0.801
Grade aGVHD	Median (range)	161	0 (0-4)	92	0 (0-4)	0.073
cGVHD, n (%)	Total	141	25 (%)	75	9 (%)	0.205
	Limited	141	3 (%)	75	3 (%)	0.377
	Extensive	141	22 (%)	75	6 (%)	0.480
TPN	Frequency	161	152 (94.7%)	92	83 (90.2%)	0.212
Duration, days	Median (range)	161	19 (0-67)	92	22 (0-56)	0.018
Mucositis						
WHO grade	Median (range)	161	2 (0-4)	92	3 (0-4)	<0.001
Duration	Median (range), days	161	9 (0-44)	89	13 (0-47)	<0.001
Severe infection	Frequency	161	79 (49.1%)	92	39 (42.7%)	0.335
Gastrointestinal hemorrhage	Frequency	161	15 (8.7%)	92	5 (5.6%)	0.380

ATG: Anti-thymocyte globulin; aGVHD: acute graft-*versus*-host disease; ANC: absolute neutrophil count; cGVHD: chronic graft-*versus*-host disease; CMV: cytomegalovirus; CR>1: second and subsequent complete remission; EBV: Epstein-Barr virus; GVHD: graft-*versus*-host disease; HCT: hematopoietic cell transplantation; MAC: myeloablative conditioning; MFD: matched familiar donor; MNC: mononuclear cells; MUD: matched unrelated donor; PB: peripheral blood; PLT: platelets; RIC: reduced-intensity conditioning; RTC: reduced toxicity conditioning; TBI: total body irradiation; TPN: total parenteral nutrition; WHO: World Health Organization.

Risk for severe GVHD. No impact of palifermin use on acute (p=0.073), limited chronic (p=0.377), extensive chronic (p=0.480) and any grade of chronic GVHD (p=0.205) was observed. In univariate analysis, the following factors increased risk for severe GVHD: Donor other than MFD/MUD (HR=4.36, 95% CI=1.70-11.2; p=0.002), diagnosis of solid tumor (HR=5.55, 95% CI=1.32-25.0; p=0.019), and OM grades III/IV (HR=2.17, 95% CI=1.16-4.16; p=0.02).

Risk for GRFS. The following prognostic factors conferred a reduced risk for GRFS: age <10 years (HR=0.68, 95% CI=0.48-0.97; p=0.035), Karnofsky/Lansky score ≥90

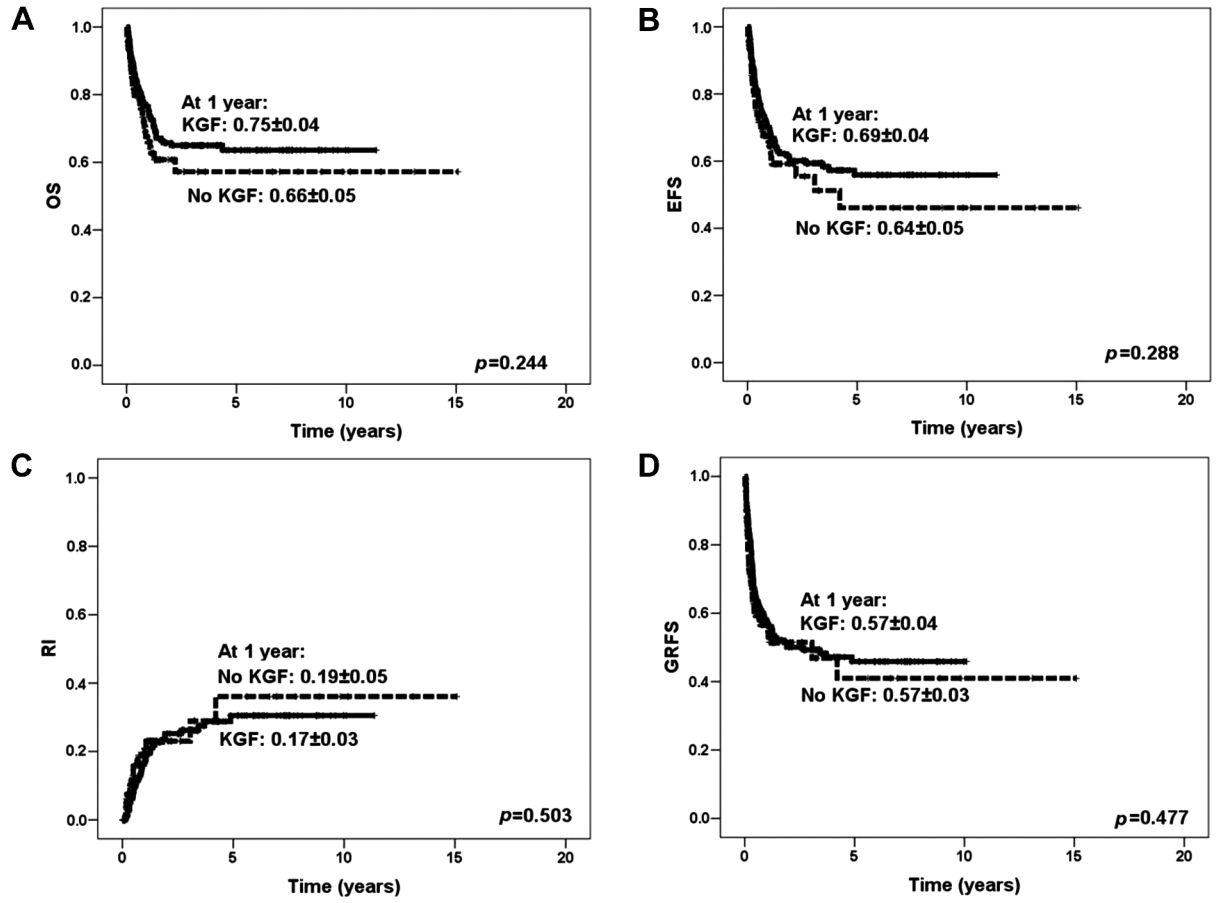

Figure 1. *Effect of keratinocyte growth factor (KGF; palifermin) on transplant outcomes: A: Overall survival (OS). B: Event-free survival (EFS). C: Relapse incidence (RI). D: graft-versus-host disease-free relapse-free survival (GRFS).*

(HR=0.42, 95% CI=0.24-0.74; p=0.003), neutrophil recovery (HR=0.22, 95% CI=0.10-0.46; p<0.001). Prognostic factors increasing risk of GRFS included: donor other than MUD/MFD (HR=2.54, 95% CI=1.29-5.01; p=0.009), diagnosis of solid tumor (HR=3.57, 95% CI=1.11-11.1; p=0.032), transplantation in CR>1 status (HR=2.04, 95% CI=1.43-2.86; p<0.001), and OM grades III/IV (HR=1.47, 95% CI=1.04-2.08, p=0.03).

Results of multivariate analyses are presented in Table II.

Discussion

In this study, we analyzed the impact of the prophylactic use of palifermin on transplant outcomes in a large cohort of children undergoing allo-HCT. Although palifermin significantly shortened the duration and grade of mucositis, no prognostic effect was found on the short- and long-term effects of transplantation. It was shown in adult patients undergoing auto- and allo-HCT due to hematological malignancies, with TBI and chemotherapy as conditioning regimen, that patients had shorter duration of OM, shorter duration of grade III or IV of OM, shorter duration of soreness of the mouth and throat, lower opioid use and lower use of total parenteral nutrition (1, 10, 17, 18).

We observed that favorable prognostic factors for OS were transplantation from MFD, good overall patient condition, and use of TBI in conditioning, while HCT in the second or subsequent remission had a negative impact. Prognostic factors for EFS were the good overall condition of the patient and age below 10 years at HCT. These results were consistent with data for adult patients (1, 17, 19-22). As in the study of Blazar *et al*. (17), we found no effect of palifermin use on the recurrence rate but did find that diagnosis of solid tumor and transplantation in CR>1 status increased the risk of relapse. No effect of palifermin on the occurrence of severe GVHD was found. However, HCT from MFD, and neutrophil reconstitution later than 18 days before HCT were favorable prognostic factors that reduced the risk

Table II. *Multivariate analyses of risk factors for outcomes of allo-hematopoietic cell transplantation (HCT).*

	OS		EFS		RI		Severe GVHD		GRFS	
Risk factor	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age at HCT <10 years	0.67 (0.48-1.28)	0.336	0.65 (0.43-0.97)	**0.035**	0.78 (0.46-1.33)	0.358	0.72 (0.38-1.35)	0.302	0.89 (0.61-1.32)	0.567
Matched family donor HCT	0.58 (0.35-0.96)	**<0.001**	0.67 (0.42-1.06)	0.094	0.94 (0.54-1.64)	0.825	0.32 (0.12-0.83)	**0.020**	0.39 (0.20-0.77)	**0.009**
Clinical stage CR>1 at HCT	2.13 (1.43-3.44)	**<0.001**	2.38 (1.59-3.57)	**<0.001**	3.85 (2.13-6.66)	**<0.001**	1.39 (0.74-2.56)	0.304	1.82 (1.26-2.63)	**<0.001**
TBI use in conditioning	0.28 (0.15-0.56)	**<0.001**	0.74 (0.45-1.23)	0.254	1.14 (0.62-2.08)	0.674	0.88 (0.41-1.92)	0.754	0.79 (0.5-1.23)	0.305
Karnofsky/Lansky score ≥90	0.37 (0.20-0.70)	**0.002**	0.41 (0.22-0.76)	**0.005**	2.38 (0.33-20.0)	0.386	1.59 (0.39-6.67)	0.518	0.52 (0.29-0.93)	**0.028**
Diagnosis of solid tumor	2.27 (0.67-7.69)	0.183	3.33 (1.07-11.1)	**<0.042**	4.54 (1.39-16.6)	**0.013**	5.26 (1.26-25.0)	**0.023**	1.92 (0.58-6.25)	0.286
Mucositis grade 3-4	1.37 (0.80-2.08)	0.148	1.61 (1.08-2.43)	**0.019**	1.37 (0.80-2.33)	0.250	2.17 (1.13-4.16)	**0.020**	1.38 (0.97-2.00)	0.070
Neutrophil recovery >18 days after HCT	0.75 (0.47-1.18)	0.206	0.79 (0.52-1.19)	0.251	0.78 (0.47-1.33)	0.357	0.50 (0.26-0.97)	**0.041**	1.03 (0.61-1.75)	0.913

CR1>1: Second and subsequent complete remission; EFS: event-free survival; GVHD: graft-*versus*-host disease; GRFS: GVHD-free relapse-free survival; HCT: hematopoietic cell transplantation; HR: hazard ratio; ns: not significant; OS: overall survival; *p*: statistical value; RI: relapse incidence; TBI: total body irradiation. Statistically significant *p*-values are shown in bold.

of severe GVHD. On the other hand, a diagnosis of solid tumor and grade III/IV OM increased the risk of severe GVHD. A lack of any protective impact of KGF on the incidence and severity of GVHD was also found in adult patients (17, 19, 23).

A new composite endpoint assessing relapse-free and severe GRFS was analyzed in this study. This composite endpoint only measures the time to the first event, and therefore cannot replace a detailed analysis of the individual events that make up the endpoint: all components that make up GRFS are extremely important for a positive outcome of HCT. We found that the use of palifermin had no effect on relapse-free GVHD-free survival, whereas in univariate analysis, the prognostic factors of GRFS were: age <10 years at HCT, transplantation from MFD, Karnofsky/Lansky score ≥90, CR1 status, and OM lower than grade III/IV. In the multivariate analysis, favorable prognostic factors for GRFS were HCT from MFD, and Karnofsky/Lansky score ≥90 at the time of HCT, while an adverse prognostic factor was CR>1 status. Holtan *et al*. found that apart from age, disease stage and type of donor, the source of hematopoietic cells influenced GRFS. The use of bone marrow as a source of hematopoietic cells was a positive prognosis factor (24). Solh *et al*. made similar conclusions in their analysis, where clinical stage of the disease, source of hematopoietic cells and donor type significantly influenced GRFS (25).

In conclusion, in this largest pediatric allo-HCT study, in spite of improving clinical course of OM, palifermin had no impact on event-free survival, risk of recurrence, OS, the incidence and severity of GVHD, nor relapse-free and severe GVHD-free survival.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Study design: KC and JS. Data analysis and interpretation: KC, JS and NB. Article writing: KC and JS. Provision of important clinical data: All Authors. Data check: All Authors. Statistical analysis: JS and KC. Administrative support: JS. Final approval: All Authors.

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