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Efficacy of keratinocyte growth factor in prevention of oral mucositis in children undergoing allogeneic hematopoietic cell transplantation

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Abstract

Introduction: Oral mucositis is regarded by patients as one of the worst and debilitating complications of conditioning and hematopoietic cell transplantation (HCT). Prevention of mucositis is one of the priorities of supportive therapy during and after conditioning. Objectives: The primary objective of the study was the analysis of efficacy of keratinocyte growth factor (KGF, palifermin) used in prophylaxis of oral mucositis in patients undergoing allo-HCT. The secondary objectives of the study included the analysis of the influence of palifermin on clinical course of oral mucositis and early transplant outcomes, as well as analysis of the contraindications of palifermin in patients undergoing allo-HCT. Patients and methods: A total number of 253 allo-HCT performed between 2003 and 2018 in patients aged 0–19 years in a single center were analyzed. Overall, in 161 HCTs, palifermin was administered. Results: Patients receiving KGF were transplanted earlier in the context of calendar year, and more often received ATG, mainly due to the higher rate of unrelated donor transplants. Allo-HCT patients who were administered palifermin had shorter time of mucositis (median: 9 vs. 13 days, $p < 0.001$), lower mucositis grade (median: 2° vs. 3°; $p < 0.001$), shorter period of total parenteral nutrition (median: 19 vs. 22 days; $p = 0.018$), and lower incidence of episodes of febrile neutropenia (median: 39.1% vs. 83.1%; $p < 0.001$). Conclusions: The use of palifermin has decreased duration and severity of oral mucositis in children after allo-HCT. Palifermin is a safe and well-tolerated compound in children undergoing allo-HCT.

Keywords:
hematopoietic cell transplantation, mucositis, palifermin, children

Introduction

Oral mucositis (OM) is a painful inflammation and ulceration of the mucous membrane. It is considered to be one of the most common problems associated with cancer and hematopoietic cell transplantation (HCT) therapy. OM is regarded by patients as one of the worst and debilitating complication of conditioning and transplantation [1, 2]. The overall incidence of OM in HCT patients is reported to be from 75% to 100% [3–7].

Almost in all patients, a severe mucositis of III/IV° is observed after myeloablative conditioning [8]. The most toxic conditioning leading to OM are total body irradiation (TBI)-based, busulfan-based, and carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning [6, 9, 10]. During conventional chemotherapy, patients with acute lymphoblastic leukemia, acute myeloblastic leukemia, and non-Hodgkin's lymphoma are at the highest risk of developing OM [9].

A number of approaches for prevention and treatment of OM have been presented in the article. In a systematic review of evaluation of the effectiveness of prophylactic agents for treating OM in patients receiving chemotherapy and/or radiotherapy, results of the total number of 10,514 randomized participants were analyzed [11]. Ten interventions were shown to have helping (albeit sometimes weak) in either prevention or reduction of the severity of mucositis when compared to either a placebo or no treatment. These interventions included administration of recombinant human keratinocyte growth factor (KGF, palifermin), cryotherapy, amifostine, granulocyte-colony stimulating factor (G-CSF), aloe vera, laser, intravenous glutamine, sucralfate, honey, and polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste [11].

Therapeutic methods for oral mucositis recommended by Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) are KGF [11, 12, 13], low-level laser light therapy (LLLT) [11,13,14], cryotherapy [11, 13, 15], benzydamine [11, 13, 16], and morphine [11, 13, 17].

In the analysis of estimating the efficacy of cytokines for preventing OM in patients receiving chemotherapy and/or radiotherapy, the only positive recommendation made was the use of palifermin before conditioning treatment and immediately after transplantation in autologous stem cell transplant setting for hematological malignancies. On the other hand, a suggestion was made against the use of mouthwash with GM-CSF for the prevention of OM in the setting of high-dose chemotherapy followed by auto- or allo-HCT. No guideline was possible for any other cytokine or growth factor agents due to inconclusive evidence [12].

Current medical knowledge suggests that palifermin when used in prophylaxis can significantly reduce frequency and intensity of mucositis in patients after TBI and/or high-dose chemotherapy, whereas other

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methods of prevention and treatment of mucositis have limited value in this painful complication.

Prevention of mucositis is one of the priorities of supportive therapy during and after conditioning. We introduced the prophylactic use of palifermin in patients undergoing HCT in our department in 2006. The primary objective of the study was the analysis of the efficacy of palifermin used in prophylaxis of OM in patients undergoing allo-HCT. The secondary objectives of the study included the analysis of the influence of palifermin on clinical course of OM and early transplant outcomes, as well as the analysis of the contraindications of palifermin in patients undergoing allo-HCT.

Patients and methods

Study design

Analysis of efficacy and safe use of palifermin on clinical course of early post-transplant period as well as palifermin's impact on short-term transplant outcomes compared to the group of HCT patients who were not treated with palifermin was performed.

Patients

A total number of 253 allo-HCT transplantations performed between 2003 and 2018 in patients aged 0–19 years in a single center were analyzed. Overall, palifermin was administered in 161 allo-HCTs.

Data collection

Collection of data was based on patients' history including assessment of oral mucositis and the ability of the patients to swallow solid food and fluids, which is required for total parenteral nutrition (TPN). Oral mucositis was assessed everyday as a routine part of physical examination. Opioid use, length of TPN use, incidence of gastrointestinal complications, severe infection, fever, engraftment, and the length of hospitalization were assessed in all patients.

After completing data collection the following information were analyzed: age, primary diagnosis, stage of disease, source and dose of hematopoietic cells, CMV and EBV serologic profile of donor and recipient, type of donor, conditioning regimen, time to neutrophil and platelet engraftment, presence of acute and chronic graft-versus-host disease (a/cGVHD), infections, TPN, and severe oral mucositis grade 3/4°. Also, patients in the study group were evaluated for the presence of adverse effects related to palifermin administration.

Grading of mucositis

Oral mucositis was assessed in 5 grades as suggested by World Health Organization (Tab. I). Grade I oral mucositis was described as patients having soreness with or without the presence of erythema. Grade II oral mucositis was defined as patients experiencing pain with the presence of erythema and ulcerations. The patient maintains the ability to swallow solid foods. Grade III oral mucositis was defined as patients experiencing severe pain and ulcers with extensive erythema. The patient is unable to swallow solids. Grade IV oral mucositis was defined as patients experiencing intolerable pain, often unable to speak, and oral alimentation is not possible. Grade III and IV oral mucositis were classified as severe. Maximum grades of oral mucositis were included in the analysis [18].

Keratinocyte growth factor administration

KGF (palifermin) was administered intravenously at the dose of 60 mg/kg/day (Kepivance, Biovitrum, Stockholm, Sweden) once daily for 3 consecutive days before the conditioning treatment and for 3 consecutive days after the transplantation starting from day 1 (a total of six doses). An interval of 24 hours was kept between the third dose and the beginning of conditioning, as well as between the end of graft infusion and the fourth dose of palifermin.

Definitions

Neutrophil engraftment was defined as the first of three consecutive days of absolute neutrophil counts exceeding 0.5 G/L. Platelet engraftment was defined as the first of three consecutive days with platelets more than 20 G/L with no platelet transfusions done during the preceding 7 days. Infections were classified as microbiologically documented infection (MDI) when pathogenic microorganism was identified; clinically documented infection (CDI) with the presence of signs and symptoms of inflammation at anatomic sites and pathogen was not identified; and fever of unknown origin (FUO) in case of fever without a localized source of infection or identified pathogen.

Supportive care

Uniform, standard anti-infective prophylaxis has been applied for patients undergoing HCT, including policies of preemptive viral approach. Empirical, preemptive, or targeted anti-infectious therapy was performed with various antifungal agents according to commonly accepted strategies [19–28]. Ciprofloxacin or cefuroxime axetil and fluconazole were applied during neutropenia unless other antibiotics or antifungals were used in therapy. Amoxicillin or cefuroxime axetil, acyclovir, and trimethoprim/sulfamethoxazole were used for anti-infectious prophylaxis after engraftment. Antifungal prophylaxis was used routinely in allo-HCT patients during neutropenic phase or immunosuppressive therapy and fluconazole was included or, rarely, other azoles up to 2014; and then posaconazole or voriconazole was used in allo-HCT patients who are in GVHD phase or for secondary prophylaxis. A commercial immunoglobulin preparations were given in case of decreased immunoglobulin concentration during the first

Table I. WHO grading of oral mucositis

Grade				
0	1	2	3	4
No symptoms	Soreness and erythema	Erythema, ulcers; patients can swallow solid diet	Ulcers, extensive erythema; cannot swallow solid diet	Mucositis to the extent that alimentation is not possible

month and then monthly until B-cell function recovery. Additionally, environmental prophylaxis was applied [29].

Bioethical issues

All patients provided standard informed consent for allo-HCT, data analysis, and publication. The study was approved by Local Bioethical Committee 591/2018.

Statistical analysis

The Mann–Whitney U-test was used for non-categorical comparisons and Chi-square or Fisher exact test for categorical comparisons. A *p*-value below 0.05 was considered statistically significant.

Results

Demographics

Total number of 253 allo-HCT (161 males, 92 females) patients were included in the analysis. In 161 transplants palifemin was used. The characteristics of the patients involved in the study are presented in table II.

Effect of palifermin on clinical course of transplantation and its complications

Patients receiving palifermin were transplanted earlier in the context of calendar year, and more often received ATG, mainly due to the higher rate of unrelated donor transplants (Tab. III). Allo-HCT patients who were administered with palifermin had shorter time of mucositis (median: 9 vs. 13 days; $p < 0.001$), lower mucositis grade (median: 2° vs. 3°; $p < 0.001$), shorter period of TPN (median: 19 vs. 22 days; $p = 0.018$), and lower number of episodes of febrile neutropenia (median: 39.1% vs. 83.1%; $p < 0.001$). No impact of use of palifermin in acute or chronic GVHD incidence was observed.

Adverse events of palifermin

In general, palifermin was well-tolerated. After its administration only 12 (7.4%) patients reported mild adverse events, including erythema or rash, pruritus, skin tenderness, or swelling of lips or tongue (Tab. IV).

Table II. Characteristics of the patients

Characteristics	n (%)
Female/Male	92 (36.4%)/161 (63.6%)
Use of KGF	161 (63.6%)
Primary diagnosis	
ALL	107 (42.3%)
AML	60 (23.7%)
SAA	35 (13.8%)
ABL	8 (3.2%)
PID	16 (6.3%)
MDS	6 (2.3%)
HD	6 (2.3%)
CML	5 (1.9%)
JMML	3 (1.1%)
Other	7 (2.8%)
Type of HCT	
MUD	162 (64%)
MFD	78 (30.9%)
MMUD	7 (2.8%)
HAPLO	6 (2.3%)
Stadium of the disease	
CR1	154 (60.9%)
CR > 1	99 (39.1%)
Conditioning	
RIC/RTC	78 (30.8%)
MAC	175 (69.2%)
TBI	51 (20.1%)
Busulfan use	119 (47.0%)
Treosulfan use	21 (8.3%)
Fludarabine use	75 (29.6%)
ATG use	136 (53.8%)
Death	86 (34%)
Progression	37 (43%)
Complications	49 (57%)
Mucositis clinical WHO scale	
0	39 (15.4%)
1	30 (11.9%)
2	66 (26.0%)
3	54 (21.3%)
4	64 (25.4%)
Analgesics used	
Opioids	187 (73.9%)
Tramadol	76 (30.0%)
Other	35 (13.9%)
Not used	76 (30.0%)
	66 (26.1%)
Other complications	
Neutropenic fever	139 (54.9%)
Pneumonia	46 (18.1%)
Blood-stream infection	117 (46%)
No severe infection	36 (14.2%)

n – number of patients; ALL – acute lymphoblastic leukemia; AML – acute myeloblastic leukemia; SAA – severe aplastic anemia; PID – primary immunodeficiencies; MDS – myelodysplastic syndromes; HD – Hodgkin lymphoma; CML – chronic myeloid leukemia; JMML – juvenile myelomonocytic leukemia; MUD – matched unrelated donor; MFD – matched family donor; MMUD – mismatched unrelated donor; CR – complete remission; RIC – reduced intensity conditioning; RTC – reduced toxicity conditioning; MAC – myeloablative conditioning; TBI – total body irradiation; WHO – World Health Organization

Discussion

KGF is the first human epithelial growth factor showing protective activity to the damage caused by chemo- or radiotherapy. It inhibits apoptosis and pro-inflammatory cytokines, making cytoprotective effect on epithelial cells expressing receptor for KGF [1, 12]. Classical indication for the use of KGF included hematological disorders qualified to myeloablative conditioning consisting of chemotherapy and TBI, before auto-HCT in adult patients [1]. In the study of Spielberger et al., patients receiving KGF compared to placebo group had shorter median duration of OM (6 vs. 9 days), median duration of severe OM III/IV° (3 vs. 9 days; $p < 0.001$), patient-reported soreness of the mouth and throat (area-under-the-curve score: 29.0 vs. 46.8; $p < 0.001$), the median use of opioids (212 vs. 535 mg of morphine equivalents; $p < 0.001$), and the rate of use of total parenteral nutrition (31% vs. 55%; $p < 0.001$) [1]. In other studies, the positive effect of palifermin was shown in adults both after auto-HCT and allo-HCT [7, 30, 31].

The experience in pediatric setting is much lower: results of two studies carried out after auto-HCT showed lower incidence of grade

Table III. Characteristics of groups of patients and impact of KGF on clinical course of allo-HCT

Characteristics	KGF		No KGF		*p*
	n	Value	n	Value	
Sex: male vs. female	161	102:59 (63.4%)	92	59:33 (64.1%)	0.901
Age, years (median, range)	161	10.7 (0.4–22.3)	92	9.9 (0.6–20.9)	0.147
Time of 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 family donor (MFD)	161	44 (27.3%)	92	35 (38%)	0.077
Matched donor (MFD + MUD)	161	151 (93.8%)	92	90 (97.8%)	0.147
Matched unrelated donor (MUD)	161	107 (66.5%)	92	45 (48.9%)	0.009
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
Stadium of disease (CR > 1)	161	66 (41.0%)	92	33 (35.9%)	0.423
Hematopoietic cell source PB: BM	161	101 (62.7%)	92	59 (64.1%)	0.744
Conditioning RIC/RTC	161	50 (31.0%)	92	29 (31.5%)	0.939
Conditioning 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
Fludarabine use	161	52 (32.3%)	92	23 (25.0%)	0.264
CMV IgG recipient	161	126 (78.3%)	92	72 (78.3%)	0.925
EBV IgG recipient	161	145 (90.1%)	92	83 (90.2%)	0.927
CMV IgG donor	161	81 (50.9%)	92	48 (52.2%)	0.775
EBV IgG donor	161	114 (70.8%)	92	62 (67.4%)	0.569
Dose MNC (10^8/kg) (median, range)	161	8.65 (0.41–53)	92	10.27 (0.34–35.3)	0.289
Dose CD34 (10^6/kg) (median, range)	160	6.41 (0.8–28.3)	92	6.66 (0.49–25.2)	0.334
Day of neutrophil engraftment ANC > 0.5 G/L (median, range)	155	18 (11–34)	73	17 (10–27)	0.229
Day of platelet engraftment PLT > 20 G/L (median, range)	140	16 (0–65)	65	14 (8–55)	0.136
Day of reticulocytes > 5‰ (median, range)	149	15 (9–43)	71	15 (12–40)	0.788
Severe GVHD (aGVHD 3/4° or extensive cGVHD)	160	25 (15.6%)	90	15 (16.7%)	0.830
Day of beginning of severe GVHD (median, range)	25	102 (15–160)	15	40 (20–120)	0.128
aGVHD grade 1–4	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 (total)	141	25 (%)	75	9 (%)	0.205
cGVHD (limited)	141	3 (%)	75	3 (%)	0.377
cGVHD (extensive)	141	22 (%)	75	6 (%)	0.480
TPN use	161	152 (94.7%)	92	83 (90.2%)	0.212
TPN (number of 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
Mucositis (days) (median, range)	161	9 (0–44)	89	13 (0–47)	<0.001
Neutropenic fever	161	63 (39.1%)	92	76 (83.1%)	<0.001
Severe infection	161	79 (49.1%)	92	39 (42.7%)	0.335
Gastrointestinal hemorrhage	161	15 (8.7%)	92	5 (5.6%)	0.380

n – number of patients; p – statistical value; TBI – total body irradiation; ATG – anti-thymocyte globulin; TPN – total parenteral nutrition; aGVHD – acute graft-versus-host disease; cGVHD – chronic graft-versus-host disease; KGF – palifermin

Table IV. Adverse events after use of palifermin

Adverse events	n (total n = 161)
Erythema	5/161 (3.1%)
Rash	3/161 (1.9%)
Pruritus	3/161 (1.9%)
Tenderness	2/161 (1.2%)
Swelling of lips and/or tongue	4/161 (2.5%)
Total	12/161 (7.4%)*

*n – number of patients; * – some patients had >1 adverse event*

III/IV° oral mucositis in patients receiving palifermin, although the other outcomes were inconclusive [32, 33]. Recently, two meta-analyses on the use of palifermin were published [3, 5]. In the analysis of Mozaffari et al. [3], including both children and adults, either after auto- or after allo-HCT, impact of palifermin was shown neither on duration and severity of OM nor on occurrence of aGVHD. On the contrary, in the study of children on conventional chemotherapy, palifermin significantly reduced incidence, duration, and severity of mucositis [5]. Findings that palifermin could be a valid therapeutic tool to improve the quality of life of children suffering from leukemia or lymphoma or undergoing HCT were confirmed by other studies [15, 34, 35, 36], although the lack of effect was also documented [7, 30, 37].

The main message from our large cohort study is that pediatric allo-HCT patients receiving palifermin had shorter time of mucositis (median: 9 vs. 13 days, $p < 0.001$), lower mucositis grade (median: 2° vs. 3°, $p < 0.001$), shorter period of TPN (median: 19 vs. 22 days, $p = 0.018$), and lesser number of episodes of febrile neutropenia (median: 39.1% vs. 83.1%, $p < 0.001$). With this study, we are confident that palifermin is beneficial for the prevention of OM in children who are receiving allo-HCT after conditioning therapy.

Our findings also bring economical value. The use of palifermin leads to decrease in TPN use and the number of episodes of febrile neutropenia, thus decreasing costs of antibiotic therapy. Although palifermin is a costly compound, it can give positive cost–benefit balance, which was also shown in other studies that indicate lower health-care resource utilization [31, 32, 37, 38]. The use of palifermin can indirectly decrease other transplant complications [31]. Nevertheless, the high cost contributed to the fact that this drug did not become a part of the standard supportive care in pediatric HCT, despite its contribution to the significantly decreased duration and severity of oral mucositis in children.

Over last twenty years, a large number of analyses on prevention and treatment of oral mucositis in patients receiving chemo- and/or radiotherapy were published in Cochrane Database of Systematic Reviews [11, 13]. Although the interpretation of all results is a complicated task, it has been found that palifermin is the most efficacious compound. Still, at present there is no particular intervention that may be regarded as the gold standard for the prevention and treatment of OM.

The use of palifermin appeared to be a safe intervention. Adverse events of its use, mainly erythema, rash, pruritus, mouth, and tongue disorders, including taste alteration, were found to be relatively mild and transient, both in our and other studies [1, 7, 30, 35, 39–41]. Based on the data from other studies [1, 7, 42] and from our experience, possible adverse events after the use of palifermin occur less frequently in children than in adults. In long-term follow-up, no adverse events that could be attributed to palifermin were observed, including development of acute myeloid leukemia, myelodysplastic syndrome, skin cancer, or decreased overall survival [12, 13, 43].

In conclusion, the use of palifermin has decreased the duration and the severity of OM in children after allo-HCT. Palifermin was a safe, well-tolerated compound for children who are treated with allo-HCT.

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Authors' contributions

JS, KC – study design. NB, KC, JS – data analysis and interpretation. NB, JS – manuscript writing. KC, JS – statistical analysis. JS – administrative support. All authors – provision of important clinical data, data check-up, final approval.

Conflict of interest

All authors declared no conflict of interest related to this study.

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Ethics

The work described in this article has been 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.

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