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Keratinocyte growth factor decreases incidence of severe oral mucositis in children undergoing autologous hematopoietic stem cell transplantation

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ABSTRACT

Introduction: Keratinocyte growth factor (palifermin) is used for the prevention of mucositis in adults following autologous and allogeneic hematopoietic stem cell transplantation (HSCT). It is known that palifermin decreases length of initial hospital stay, mean number of days of total parenteral nutrition and the use of opioids for pain control in oral mucositis in adults. There are limited data evaluating palifermin use in children following autologous HSCT.

Aim: The aim of this study was to analyze the efficacy and safety of palifermin in children and adolescents following autologous HSCT.

Material and methods: The study included 81 consecutive patients. Results of efficacy and safety of palifermin in 18 patients were compared to data of 63 patients not treated with palifermin.

Results and discussion: Palifermin decreased the incidence of severe oral mucositis (grade 3–4 WHO) by 19% (44% vs. 63%), however it did not contribute to the duration of oral mucositis and total parenteral nutrition use. There were no differences in opioid use, incidence of fever of unknown origin, severe infection, engraftment and gastrointestinal hemorrhage between groups. Five-year overall survival was better in patients treated with palifermin. Only in one patient generalized, itching rash was observed after palifermin administration.

Conclusions: Palifermin decreases incidence of severe oral mucositis and improves overall survival in children undergoing autologous HSCT.

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1. Introduction

High-dose chemotherapy and radiotherapy followed by hematopoietic stem cell transplantation (HSCT) is a well-established treatment for hematologic cancers. The incidence and severity of oral mucositis (OM) vary with the conditioning regimen.[1] OM affects from more than 75% of patients undergoing chemotherapy[2] up to 98% of patients undergoing myeloablative therapy and HSCT.[3] Typically OM peaks between days 6–12, and begins to resolve by days 14–18 after transplantation.[4] The risk factors of OM incidence include the use of chemotherapeutic agents such as methotrexate, fluorouracil, etoposide, melphalan and cytarabine.[4] Total body irradiation (TBI) has also been associated with increased risk of developing mucositis in various oncology patient populations.[4,5] In the pediatric population, underlying disease and chemotherapy regimens are the principal risk factors of OM development.[6] The preferred regimen for the prevention of OM for patients receiving HSCT remains unclear.[7] A number of studies have attempted to evaluate different agents or strategies to prevent or treat mucositis associated with high-dose chemotherapy, with conflicting results.[7]

Mucosal lesions develop as a result of activity of chemotherapeutic agents in rapidly dividing cells of the gastrointestinal tract.[2] OM severity can range from mild, painless tissue changes to bleeding ulcerations that prevent oral intake and require narcotic pain relievers.[2] Sonis et al. reported that mucositis is correlated with an increased risk of infection, mortality, days of injectable narcotics, and hospital stay what increase the total cost of hospitalization.[8]

Keratinocyte growth factor (KGF) was first described as a growth factor for epithelial cells and has demonstrated protection against chemotherapeutic or radiation injury.[9] Palifermin, a recombinant human KGF (rHuKGF), specifically stimulates the growth and anti-apoptotic potential of epithelial cells expressing the KGF receptor without directly affecting non-epithelial cells lacking this receptor.[9] Palifermin can significantly reduce the duration and incidence of OM after intensive chemotherapy and radiation and autologous HSCT in adults.[1,10] However, published clinical and pharmacokinetic data on palifermin use in children and adolescents are limited, and palifermin dosing has not been established in the pediatric setting.[11] Currently, there is no consensus for the prevention and treatment of severe OM in adults and in pediatric population.

2. Aim

The objective of this study was to analyze the efficacy and safety of palifermin in children and adolescents before and after autologous HSCT.

3. Material and methods

3.1. Patients

The study included 81 consecutive patients undergoing autologous HSCT between 2004 and 2012. Efficacy and safety of palifermin were assessed in 18 patients and compared with data of 63 patients not treated with palifermin. Baseline characteristics of the patients and conditioning regimen are shown in Table 1. The stem cell source was peripheral blood ($n = 78$) or bone marrow ($n = 3$).

3.2. Methods

Palifermin was administered intravenously at the dose of 60 μg/kg (Kepivance, Biovitrum) once daily during 3 consecutive days before the conditioning treatment and for 3 consecutive days after the transplantation starting from day 0 (a total of six doses). Standard procedures related to conditioning regimen and supportive therapy were used in all patients. Ciprofloxacin or cefuroxime axetil, fluconazole, acyclovir, trimethoprim/sulfamethoxazole were used for anti-infection prophylaxis. Indication for red blood cells transfusion was hemoglobin concentration lower than 80 g/L. Indications for platelets transfusion were active bleeding and/or PLT lower than 20×10^9/L. Betalactam antibiotics were used as a frontline therapy in neutropenic fever, if not contraindicated. Filgrastim was administrated subcutaneously if no white blood cells recovery after day +12 was observed or if the amount of $CD34^+$ cell per kilogram body weight was lower than 5×10^6 or transplant program required. For mucositis-related pain control drugs according to the analgesic ladder were used. To reduce OM-related discomfort cold drinks, mount cooling or local anesthetics were used that was dependent on patient preferences. Total parenteral nutrition was implemented when the patient did not take food or fluids orally or enteric nutrition was contraindicated for more than 1 day. In contrast, total parenteral nutrition was terminated when the patient ingested proper quantity of food to ensure normal functioning.

In the palifermin group each patient was assessed for the presence of adverse events related to palifermin

Table 1 – Patients characteristics.

	Patients treated without palifermin ($n = 63$)	Patients treated with palifermin ($n = 18$)	P value
Sex (male/female)	37/26	12/6	0.738
Age, years; median (range)	13.2 (1.0–19.8)	6.3 (0.7–17.1)	0.117
Weight, kg; median (range)	34 (8.0–137.0)	18.7 (8.5–67.0)	0.207
Diagnosis			
Neuroblastoma	20	8	0.317
Other solid tumors	27	4	0.112
Leukemia/lymphoma	16	6	0.504
Conditioning regimen			
Busulfan-based	27	8	0.560
Melphalan-based	15	5	0.761
Thiotepa-based	14	1	0.170
Carboplatin-based	5	3	0.367
TBI-based	2	1	0.534

TBI – total body irradiation.

administration. All patients were evaluated by two physicians for the presence of OM in 5-grade scale of World Health Organization.[12] Morphine use, length of total parenteral nutrition (TPN), incidence of gastrointestinal hemorrhage, severe infection, fever, engraftment and length of hospitalization were assessed in all patients.

3.3. *Statistical analysis*

Mann–Whitney *U*-test was used for non-categorical comparisons and χ^2 or Fisher's exact test for categorical comparisons. Probabilities of disease free survival (DFS) and overall survival (OS) were estimated by the Kaplan–Meier method and compared by the log-rank test. Risk factor analysis was performed in Cox model. A *P* value below 0.05 was considered statistically significant.

3.4. *Ethical approval*

The study was approved by the Local Bioethics Committee.

4. Results

There were no differences in basic characteristics between analyzed groups (Table 1). In the palifermin group the incidence of severe OM (grade 3–4, WHO) was reduced by 19% (44% vs. 63%, *P* = 0.2). Palifermin use did not contribute to the length of severe OM (grade 3–4, WHO) and TPN administration. There were no differences between groups in opioid use, incidence of fever of unknown origin (FUO), severe infection day of engraftment and gastrointestinal hemorrhage. In both groups there were similar length of hospitalization after transplantation (Table 2). The probability of 5-year DFS was better in patients treated with palifermin (0.94 vs. 0.37, *P* = 0.005), as well as 5-year OS (0.94 vs. 0.52, *P* = 0.028) (Fig. 1). In univariate analysis, the use of palifermin was a positive risk factor for DFS (*P* = 0.038, HR = 31, 95% CI = 1.5–1103), and it almost reached significant level for OS (*P* = 0.059, HR = 6.8, 95% CI = 0.9–50). Only in one patient generalized, itching rash was observed, and no other side effects were observed after palifermin administration.

5. Discussion

OM is a common complication associated with treatment of cancer that does not have definitive guidelines for management in the pediatric population.[2] Since it has been shown that children are at a higher risk for mucositis than adults,[2] this issue requires special attention for pediatricians. As a consequence of damage to the oral, esophageal, gastric, and colonic mucosa, HSCT recipients may require i.v. analgesia and TPN.[10] In the opinion of patients who underwent HSCT, OM is the most debilitating complication.[13]

It has been shown that palifermin given at the dose of 60 μg/kg once daily (total six doses) can effectively reduce the incidence, severity and duration of OM, and its consequences in TBI- and non-TBI-based auto- and allografts without adverse influence on engraftment in adults.[3] Data on palifermin use in pediatric population are very limited.[14,15]

In pediatric acute lymphoblastic leukemia patients conditioned with TBI and cyclophosphamide before allo-HSCT, Lauritano et al. observed statistically significant reduction in the duration of mucositis and the average grade of mucositis.[15] Blazar et al. in adult and children allograft recipients observed that palifermin use was associated with reduced incidence and mean severity of mucositis in patients conditioned with cyclophosphamide and TBI but not cyclophosphamide and busulfan.[9] Similar results were observed by the Goldberg et al., where palifermin was efficacious in recipients of TBI-based but not chemotherapy-based allogeneic HSCT.[5] Nasilowska-Adamska et al. described that in adult patients with hematological diseases undergoing HSCT the incidence of OM grades 1–4 was reduced by 30.6% (63.8% vs. 94.4%, *P* = 0.031). The mean duration of any grade of OM was 7.5 days (range 0–16) in the palifermin group and 11.5 days

Table 2 – Impact of palifermin on clinical data.

	Patients treated without palifermin (*n* = 63)	Patients treated with palifermin (*n* = 18)	*P* value
OM cases, grade 3–4, *n* (%)	40 (63)	8 (44)	0.238
Duration of OM in days, *n* (median, quartiles)	7 (6–9)	6.5 (5.0–8.8)	0.430
Opioid use, *n* (%)	5 (7.9)	2 (25.0)	0.648
Duration of TPN in days, *n* (median, quartiles)	16 (12–19)	15 (7–34)	0.613
Severe infection, *n* (%)	7 (11.1)	2 (25.0)	0.999
Fever, *n* (%)	42 (66.6)	12 (67.0)	0.988
Gastrointestinal hemorrhage, *n* (%)	4 (6.3)	2 (25.0)	0.610
Number of days after HSCT to achieve[a]			
PLT > 20×10^9/L	12 (10–16)	11.5 (10–42)	0.900
PLT > 50×10^9/L	15 (14–28)	15 (10–80)	0.403
WBC > 1×10^9/L	12 (11–13)	11 (9–22)	0.565
ANC > 0.5×10^9/L	12 (11–14)	13 (9–27)	0.581
RET > 5‰	12 (11–14)	14 (10–40)	0.305
Length of hospitalization after HSCT, in days[a]	24 (22–30)	24 (7–38)	0.641

TPN – total parenteral nutrition; PLT – platelet count; WBC – white blood cells; ANC – absolute neutrophil count; RET – reticulocytes.
[a] Numbers are given as *n* (mean, quartiles).

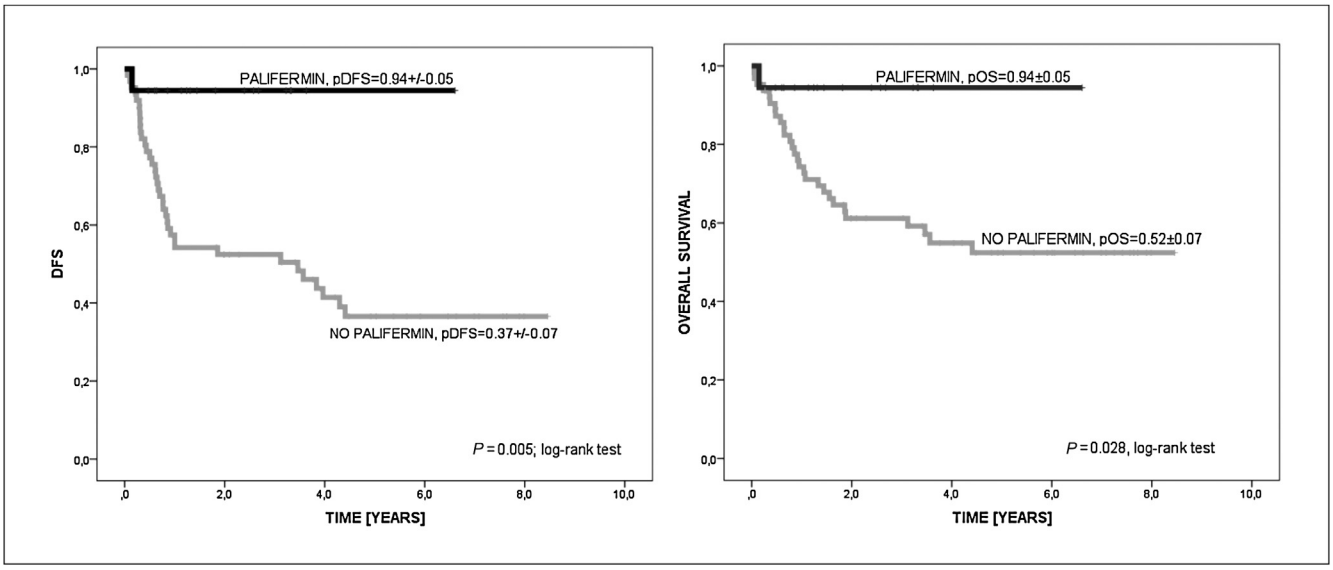

Fig. 1 – pDFS and pOS with respect to palifermin use.

(range 0–28) in the control group ($P = 0.022$).[3] Despite that, Blijlevens et al. compared palifermin use in adult patients with multiple myeloma undergoing autologous HSCT with high dose melphalan in conditioning.[16] Palifermin was unable to reduce OM or OM-related patient's burden in multiple myeloma transplant patients.[16] In adolescents and adults patients with sarcoma who received multicycle chemotherapy, palifermin reduced the cumulative incidence of moderate to severe mucositis (grade 2 or higher) and severe mucositis (grade 3 or 4),[17] however palifermin was administrated as 180 μg/kg intravenously as a single dose 3 days before chemotherapy in each cycle.

In our study, we administrated palifermin in the dose 60 μg/kg for three consecutive days before conditioning and for 3 consecutive days just after transplantation. We observed that in the palifermin group the incidence of severe OM (grade 3–4) was reduced by 19%. Majority of our patients were treated with chemotherapy. We did not observe a reduction in duration of TPN. On the other hand, several groups observed that the duration of TPN was significantly shortened by reduction in mucositis severity in palifermin group.[1,15] Patients who received palifermin had shorter requirement for TPN, however only for those conditioned with TBI.[5] This benefit was not observed in adult patients undergoing auto-HSCT for multiple myeloma.[16]

We did not observe palifermin influence on opioid use in pain control in children. Goldberg et al. observed that the benefit of palifermin in requirements for narcotics was limited to patients who received TBI.[5] Blijlevens et al. found that the use of opioids was lower in the group of patients who received palifermin before and after chemotherapy and in the group with palifermin use before chemotherapy compared with the placebo group.[16] In Spielberg et al. study, palifermin recipients used less parenteral or transdermal opioid analgesics for mucositis than did placebo recipients.[1]

In our study there were no differences between the groups in incidence of FUO and severe infection. Also, Vadhan-Raj et al. did not observe differences in incidence of FUO.[17] Besides that, in Spielberger et al. study, palifermin recipients had a lower incidence of febrile neutropenia (75% vs. 92%) and a trend toward a lower incidence of blood-borne infections (15% vs. 25%) than placebo recipients.[1] However Blijlevens et al. found that the incidence of febrile neutropenia was higher among patients who received palifermin before and after chemotherapy (34%) than before chemotherapy (25%) or placebo (26%), while the mean duration of febrile neutropenia did not differ between groups.[16] In this study, more infections were reported in patients who received palifermin before and after chemotherapy than in the placebo group (52% vs. 27%).[16]

As in other studies we did not observe any influence of palifermin on hematological recovery after transplantation.[1,9] With respect to adverse events, only in one patient we observed generalized, itching rash after palifermin use. No other side effects were observed, but there were some, such as cough, edema, taste alteration or arthralgia in other studies.[1,9,15]

6. Conclusions

Palifermin decreases severity of OM and improves overall survival in children undergoing autologous HSCT. However, the use of this drug is limited by high cost. Further investigation in pediatric population are warranted.

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Conflict of interest

There are no financial or other relationship considerations that could lead to any conflict of interest.

Authors declaration

The authors of this manuscript declare that they have complied with the Principles of Ethical Publishing present in the Declaration of Helsinki.

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