Palifermin in Children Undergoing Autologous Stem Cell Transplantation: a Matched-pair Analysis

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Abstract. *Background: Keratinocyte growth factor (palifermin) is used for 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 (TPN) 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 objective of the present study was the analysis of efficacy and safety of palifermin in children undergoing auto-HSCT. Patients and Methods: This matched-pair analysis study included 62 pediatric patients undergoing first auto-HSCT receiving palifermin on a compassionate-use basis (study group, n=31) or not (control group, n=31). Results: Palifermin decreased the incidence of severe (grade 3-4 WHO) oral mucositis (p=0.041), length of hospitalization (p=0.047) and contributed to the shorter duration of oral mucositis (p=0.035) and lower incidence of clinically or microbiologically documented infections (p=0.038). There were no differences between groups in opioid use, neutrophil and platelet recovery, TPN use and gastrointestinal hemorrhage. Conclusion: Palifermin decreases the incidence and severity of oral mucositis in children undergoing autologous HSCT.*

Autologous hematopoietic stem cell transplantation (auto-HSCT) is a well-established treatment for various types of malignant disorders. Oral mucositis (OM) is a major contributing factor to morbidity and is regarded as the most debilitating side-effect identified in patients undergoing HSCT (1). The incidence and severity of OM vary with the conditioning regimen and affects up to 98% of patients undergoing myeloablative therapy and HSCT (1, 2). 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 (3). Palifermin is a recombinant human keratinocyte growth factor known to protect epithelial cells against chemotherapeutic or radiation injury (4). Palifermin can significantly reduce the duration and incidence of OM after allogeneic HSCT in adults (1). The use of palifermin has been recommended to decrease severe mucositis in an auto-HSCT setting for hematologic malignancies in adults with total-body irradiation (TBI) conditioning regimens and considered for patients undergoing myeloablative allogeneic SCT with TBI-based conditioning regimens (5). On the other hand, published clinical and pharmacokinetic data on palifermin use in children and adolescents are limited (6, 7). The objective of the present study was the analysis of efficacy and safety of palifermin in children undergoing auto-HSCT.

Patients and Methods

Patients. This retrospective matched-pair analysis study included 62 pediatric patients undergoing first auto-HSCT receiving palifermin on a compassionate-use basis (study group, n=31) or not (control group, n=31). Patients in each group were diagnosed for lymphoma (NHL/HD, n=11), neuroblastoma (NBL, n=10) or other solid tumors (ST, n=10). There were no differences in basic characteristics between analyzed groups with respect to sex (male/female, 19/12 *vs*. 16/16, p=0.44), age (median, 10.4 *vs*. 13.2 years, p=0.42) and weight (median, 33 *vs*. 45 kg, p=0.40).

Matched population. The patients in the study group were matched and compared to a historical population followed and treated at the same hospital with the only difference of not receiving palifermin. The matching analysis takes into account sex, age, weight, diagnosis, disease status and conditioning. All patients received myeloablative conditioning and the regimen was disease-dependent: NBL patients were treated with BuMel (busulfan, melfalan),

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Table I. *Impact of palifermin on clinical data.*

	Palifermin	Control	*p*-Value
Number of patients	31	31	
Oral mucositis, grade 3-4 (n (%))	13 (42%)	21 (68%)	0.041
Duration of oral mucositis, grade 3-4 (days) (median, range)	6 (5-8)	8 (6-12)	0.035
Opioid use (n (%))	2 (6.5%)	7 (23%)	0.071
TPN administration	27 (87%)	30 (97%)	0.161
TPN (days) (median, range)	15 (7-34)	16 (12-19)	0.613
Fever (n (%))	16 (52%)	23 (74%)	0.065
CDI/MDI infection (n (%))	2 (6.5%)	8 (26%)	0.038
Blood-stream infection (BSI)	0 (0%)	3 (10%)	0.075
Gastrointestinal hemorrhage (n (%))	1 (3%)	4 (13%)	0.161
ANC>500 cells/mm^3 (days after HSCT) (median, range)	13 (8-27)	13 (9-24)	0.923
PLT>20.000 cells/mm^3 (days after HSCT) (median, range)	12 (10-42)	12 (7-49)	0.581
RET>5‰ (days after HSCT) (median, range)	13 (10-40)	12 (8-28)	0.305
Length of hospitalization (days after HSCT) (median, range)	22 (17-38)	24 (18-60)	0.047

TPN, Total parenteral nutrition; ANC, absolute neutrophil count; PLT, platelet count; RET, reticulocytes; *p*-value, statistical significance.

lymphoma patients with BEAM (BCNU, etoposide, adriamycin, melfalan) conditioning and patients with solid tumor received conditioning based on thiotepa or carboplatin. The stem cell source was peripheral blood in all patients. None of the patients underwent prior radiation.

Palifermin administration. Palifermin was administered intravenously at the dose of 60 μg/kg (Kepivance, Biovitrum, Stockholm, Sweden) 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).

Clinical data. All patients were assessed by two physicians for the presence of OM in 5-grade World Health Organization (8). The patients in the study group were evaluated for the presence of adverse events related to palifermin administration. Opioid use, length of total parenteral nutrition (TPN), incidence of gastrointestinal hemorrhage, severe infection, fever, engraftment and length of hospitalization were assessed in all patients.

Definitions of main research variables. Oral mucositis was graded daily according to the World Health Organization classification by the bone marrow transplant physicians (8). Grade I oral mucositis was described as having soreness with or without the presence of erythema. Grade II oral mucositis was defined as patients experiencing pain and with 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 Grade IV oral mucositis were classified as severe. Maximum grade of oral mucositis was included in the analysis.

Neutrophil recovery was defined as the first day of three consecutive absolute neutrophil counts greater than 500 cells/mm^3. Time to platelet recovery was defined as the first day post-nadir when platelets greater than 20.000 cells/mm3 without transfusions during the previous 7 days. Fever was defined as axillary or oral temperature >38˚C on two measurements taken one hour apart or single temperature of 38.3˚C and above. Infections during neutropenia were classified as: microbiologically documented infection (MDI) when pathogenic microorganism was recovered; clinically documented infection (CDI) with the presence of signs and symptoms of inflammation at anatomic sites and non-recovered pathogen; fever of unknown origin (FUO) in case of fever without a localized source of infection or identified pathogen. Blood stream infections were defined as a positive blood culture excluding *Staphylococcus epidermidis*.

Supportive care. Standard procedures related to conditioning regimen and supportive therapy were used in all patients (9). Ciprofloxacin or cefuroxime axetil, fluconazole, acyclovir and trimethoprim/sulfamethoxazole were used for anti-infection prophylaxis.

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

Results

The incidence of severe OM (p=0.041) and the length of severe OM (p=0.035) were significantly lower in the palifermin group (Table I). There were no differences between groups in opioid use, day of neutrophil and platelet recovery, incidence of gastrointestinal hemorrhage and incidence of fever during the first 30 days following HSCT, however, CDI/MDI occurred less frequently (p=0.038) and no BSI was diagnosed in the palifermin group. The median

length of hospitalization after HSCT was shorter by 2 days in the palifermin group (p=0.047). No significant differences were found in any sub-groups of patients.

All patients, but one, survived for 100 days after HSCT. The only death occurred due to veno-occlusive syndrome in the palifermin group. The probability of 3-year OS was similar in palifermin and control groups (0.96±0.03 *vs*. 0.96±0.03, p=0.94), as well as 3-year DFS (0.85±0.08 *vs*. 0.86±0.06, p=0.84). Palifermin was well-tolerated and after its administration only one patient presented with generalized rash, while no other side-effects were reported.

Discussion

In this study we showed that the administration of palifermin during auto-HSCT in children results in both a lower incidence of OM and shorter duration of hospitalization, contributing to better utilization of healthcare resources. In the opinion of patients who underwent HSCT, OM is the most debilitating complication (10). The use of palifermin can partially attenuate these effects and provide a better quality of life.

None of our patients was treated with radiotherapy prior to auto-HSCT. In the study of Goldberg *et al*., palifermin was efficacious in recipients of TBI-based (Total Body Irradiation), but not chemotherapy-based allo-HSCT (11). On the other hand, in the study of adolescents and adults patients with sarcoma who received multicycle chemotherapy, palifermin reduced the cumulative incidence of moderate to severe mucositis (12); however, palifermin was administrated as 180 μg/kg intravenously as a single dose 3 days before chemotherapy in each cycle.

We observed lower incidence of FUO and severe infections in the palifermin group, which seems to be an important issue. Spielberger *et al*. also have shown that 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). This observation was not confirmed in the study of Blijlevans *et al*. who 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%) (13).

The use of palifermin in the future will be dependent on its efficacy (1), cost (7) and introduction of new treatment modalities (14, 15). Palifermin was safe to all patients in our study. Some authors reported mild side-effects, such as cough, edema, taste alteration or arthralgia (1, 4, 16). No adverse effect of palifermin was observed on hematological recovery after transplantation. Currently, it is difficult to assess the role of palifermin on the use of analgesia and TPN in children, as pediatricians often tend to administer them pre-emptively as a standard of children care.

In conclusion, palifermin decreases severity and length of oral mucositis and shortens the length of hospitalization in children undergoing auto-HSCT. However, since the use of this drug is limited by high cost, further investigations in the pediatric population are necessary in order to assess healthcare utilization.

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