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Original Research Article

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.