Original Article

Palifermin and Chlorhexidine Mouthwashes in Prevention of Chemotherapy-Induced Mucositis in Children with Acute Lymphocytic Leukemia: a Randomized Controlled Trial

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ABSTRACT

Statement of the Problem: Over the past three decades, significant improvements have been achieved in the survival of children with cancer. However, the considerable morbidity which occurs as a result of chemotherapy often restricts the treatment intensity. One of the important dose-limiting and costly adverse effects of cancer therapy is mucositis. Children with hematological malignancies are greatly at risk of developing mucositis.

Purpose: This study aimed to assess the effectiveness of palifermin in preventing mucositis in children with acute lymphocytic leukemia (ALL) who undergo chemotherapy.

Materials and Method: In this clinical trial, 90 children with ALL were randomized to receive chlorhexidine (n=45) or palifermin (n=45). One group received 60 μg/ kg/ day palifermin as an intravenous bolus once daily for 3 days before and 3 days after the chemotherapy. Chlorhexidine mouthwash was administered once daily for 3 days before and 3 days after the chemotherapy. The world health organization (WHO) oral toxicity scale was employed for grading the mucositis. The data were analyzed by using two-way ANOVA.

Results: The two groups were matched for age and gender. The study groups were significantly different in terms of mucositis grading (P values after 1 and 2 week therapy were 0.00). Palifermin decreased the incidence and severity of chemotherapy-induced mucositis.

Conclusion: Palifermin reduces the oral mucositis in children with ALL. Several mechanisms of action are suggested for keratinocyte growth factor (such as palifermin) including promotion of cell proliferation and cytoprotection, restraining the apoptosis, and changing the cytokine profile.

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Introduction

All over the world, the types of cancer that are seen in children are different from those in adults. Leukemia, lymphoma, and brain tumors are the common cancers in children. [1] Over the past three decades, significant improvements have been made in the survival of children with cancer. [2] Chemotherapy, irradiation, and bone marrow transplantation are the most common

treatment of acute leukemia. [1] Despite the advances in cancer therapy, clinically significant side effects and considerable morbidity as a result of chemotherapy, often, restrict the treatment intensity. [2] Occurrence of complications in the oral cavity is independent of the chemotherapy protocol. One of the important, dose-limiting, and costly adverse effects of cancer therapy is mucositis. [3] This ulcerative lesion is painful and restricts the oral intake. It may also be a major risk factor for systemic infection which might happen due to concomitant neutropenia that occurs following chemotherapy-induced bone marrow suppression. [3]

Children are three times more prone to develop mucositis than the elderly adults, because they typically have a higher proliferation rate of basal cells. [3] Since the hematological malignancies are more likely to cause lesions than the solid tumors, [3] children with hematological malignancies have a great risk of developing mucositis.

To find the ways of amelioration of mucositis, it was shown that local therapies of mucositis with topical agents only temporary relieved the symptoms with limited success. [4]

In 2004, palifermin, a kind of keratinocyte growth factor (KGF), was approved by the United States food and drug administration (FDA) to reduce the incidence and duration of oral mucositis induced by myeloablative therapy in patients with hematological malignancies. [4]

A few studies were done to evaluate the palifermin in children. [5-6] The current study was designed to assess the effectiveness of palifermin in children with acute lymphocytic leukemia (ALL) who undergo chemotherapy.

Materials and Method

This clinical trial was approved by the Ethics Committee of Tabriz University of Medical Sciences. The induction chemotherapy protocol consisted of standard risk B-precursor ALL (COG)/ dexamethasone, vincristine, L-asparaginase, intrathecal (methotrexate+ara-C+hydrocortisone). The intensification protocol was dexamethasone, vincristine, L-asparaginase/ dexamethasone, cyclophosphamide/6-thioguanine+ cytarabine + intrathecal methotrexate.

Consent was obtained from the children's parents and assent was obtained from all children above 7 years old. A total of 90 patients aged 5 to 18 years old were randomized to receive chlorhexidine (n=45) or palifermin (n=45).

We included patients aged 5-18 years who were diagnosed with ALL and scheduled to receive chemotherapy for ALL for the first time. The exclusion criteria were having any systemic disease except ALL, presence of oral mucositis or other oral lesions before chemotherapy (assessed by an oral and maxillofacial medicine specialist other than the researchers), history of dermatology or respiratory hypersensitivity, and history of ALL recurrence. The study was registered at Iranian registry of clinical trials (IRCT2013021812510 N1) which is a primary registry in the WHO registry network setup.

Each patient was instructed to brush the teeth by using a soft brush after every meal and avoid spicy foods. The patients were randomly assigned to the palifermin or control group by using the table of random numbers.

In the study group, 60 μg/kg/day palifermin was administered as an intravenous bolus once daily for 3 consecutive days before and 3 consecutive days after the chemotherapy. In the control group, chlorhexidine was administered for 3 days before, and three consecutive days after the chemotherapy. The patients were asked to use chlorhexidine mouthwash once daily for 1 minute. This limited use of chlorhexidine was to prevent the adverse effects like tooth discoloration and temporally taste changes.

Prior to chemotherapy, the oral health was assessed by an oral and maxillofacial medicine specialist other than the researchers. Each patient was evaluated for oral lesions one and two weeks after the chemotherapy completion by the same specialist who was blind to the type of treatment.

The oral cavity assessments were performed based on the WHO oral toxicity scale for grading mucositis. The WHO scale rates mucositis from 0 to 4. Accordingly, grade 0 shows no symptom of oral mucositis, and grade 1 is characterized by soreness ± erythema. In grade 2, there are erythema and ulcers, while the patient can swallow solid food. In grade 3, there are ulcers with extensive erythema and the patient cannot swallow solid food. Grade 4 is

characterized by extensive mucositis that alimentation is not possible. [7]

Statistical analysis

Statistical analysis was performed by using SPSS software version 15. Two-way ANOVA was conducted to compare and analyze the variables of the two groups. P value< 0.05 was considered statistically significant.

Results

This investigation randomly assigned 90 subjects to receive palifermin (n=45) or chlorhexidine mouthwash (n=45). The chemotherapy doses were the same in both groups. The two groups were gender- and age-matched (Table 1).

Table 1: Characteristics of groups

	Palifermin	Control	P value
Age	8.8 (± 2.5)	8.4 (±2.2)	$p > 0.05$
Gender (F/M ratio)	23/22	23/22	$p > 0.05$

One week after the chemotherapy, grade 0 and 1 oral mucositis was observed in 97.8% of subjects (44 patients) in palifermin group and 13.3% of participants in the control group (n=6) (Table 2). Mucositis grade 2 or higher was observed in 2.2% of palifermin group participants (n=1), and 86.7% (n=39) of the control group patients (Table 2).

Two weeks after the chemotherapy, grade 0 and 1 oral mucositis was observed in 88.9% of palifermin subjects (n=40) and 8.8% of the control participants (n=4) (Table 2). Grade 2 or higher mucositis was observed in 11.1% of participants in palifermin group (n=5), and 91.1% of the controls (n=41) (Table 2).

Mann-Whitney U test showed significant results, 159.5 in one week (p= 0.00) and 110.5 in two weeks after the therapy (p= 0.00).

Regarding the adverse effects, two patients reported knee joint pain, skin rash was observed in one patient, two patients had abnormal taste, and one showed lingual mucosal thickening.

Discussion

To the best of the authors' knowledge, this was the first clinical trial which evaluated the effectiveness of palifermin in chemotherapy-induced mucositis in children with ALL. A recent case-control study reported the effectiveness of palifermin in radiation-induced mucositis in children with ALL. [6]

One of the most important non-hematological toxicities in cancer patients is mucositis. Mucositis is associated with significant morbidities, reduced food intake, higher use of narcotic pain medications, hospitalization, and risk of infections which considerably influence the quality of life. [4] Despite the numerous investigations conducted over the past years, there is no standard and effective therapy to control this common side effect in majority of cancer patients who are undergoing treatment. [4] The incidence and severity of mucositis is determined by various factors including the patient's age, gender, body mass, cancer diagnosis, drug or radiation schedule, drug choice and dose, and a range of genetic factors. [8]

Children are more at risk of developing mucositis due to the more rapid epithelial mitotic rate and more epidermal growth factor receptors. [1] Oral mucositis in children can cause pain, and consequently leads to use of analgesics, hospital admission, decreased oral intake, and also an increased risk of sepsis. [9]

Several factors are responsible for this type of oral mucositis which occur in children with leukemia compared to those with acute leukemia that exhibit without symptoms of oral mucositis. These factors are diminished level of S-IgA, myeloperoxidase, salivary peroxidase, and decreased level of proteomics in saliva into nearly half of its normal level. [9]

Improvements in understanding the pathobiology of mucositis and attempts to minimize its incidence and

Table 2: Mucositis grade of palifermin and control group

Mucositis Grade	0	1	2	3	4
Palifermin					
1 week after therapy	36 (80%)	8 (17.8%)	1 (2.2%)	0	0
2 week after therapy	16 (35.6%)	24 (53.3%)	5 (11.1%)	0	0
Control					
1 week after therapy	5 (11.1%)	1 (2.2%)	39 (86.7%)	0	0
2 week after therapy	2 (4.4%)	2 (4.4%)	1 (2.2%)	8 (17.8%)	32 (71.1%)

severity include the use of epithelial growth factors. Palifermin is a recombinant human keratinocyte growth factor, which is administered for hematological malignancies to prevent oral mucositis in patients undergoing chemo/radiotherapy. [10] There are several mechanisms of action suggested for KGF including promotion of cell proliferation and cytoprotection, restraining the apoptosis, and changing the cytokine profile. Following injury, the endogenous KGF is upregulated and may play an important role in the healing process. [4]

In this study, palifermin reduced the oral mucositis in children with ALL. Primarily, the mitogenic effect of palifermin leads to tissue protection capacity, which increases the thickness of mucosal epithelium. [5, 11] Cytotoxic therapy with extensive tissue injury can cause generation of reactive oxygen species (ROS), which subsequently damages the cells and tissues, triggers a cascade of inflammatory pathways, and stimulates the macrophages. [12] Conversely, palifermin increases the expression of Nrf2 (nerve growth factor-2) transcription factor in keratinocytes, which in turn, upregulates the genes encode a sequence of reactive oxygen species scavenging enzymes. [11]

Chemotherapy, in particular, leads to release of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) from the epithelium. TNF not only causes tissue damage, but may also be an accelerating and initiating event in the mucositis process. Likewise, IL-1 increases the subepithelial vascularity that may augment the local levels of cytotoxic agent. [3, 7, 13] Palifermin stimulates the generation of the anti-inflammatory cytokine interleukin-13 (IL-13) which reduces TNF and interfere with the mucositis process. Furthermore, there is evidence that KGFs such as palifermin can down-regulate other cytokines including transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) to reduce the inflammatory responses. [13, 15] Another positive effect of palifermin is immune reconstitution which is an important goal of allogeneic transplantation. *In vitro* studies have confirmed that KGF plays important functions in T cell homeostasis and immune improvement, by regulating the differentiation and proliferation of thymic epithelium. [4]

Among the several scales used for mucositis evaluation, this study employed the WHO scale which is commonly used in clinical trials and can assess both objective findings (like ulceration and redness) and functional data (like inability to eat food). [10]

There are some concerns about the systemic use of KGFs. Because many epithelial tumors express FGFR2b and palifermin is a mitogen for epithelial cells, potential concerns exist about promoting the epithelial tumorigenesis by palifermin. However, none of these adverse effects are reported in clinical studies and this concern is not applicable to tumors other than epithelial ones like hematopoietic malignancies. [4] One of the limitations of this study was absence of long-term follow-up. The adverse effects observed in this study was a few cases of knee joint pain, skin rash, abnormal taste, and one case of lingual mucosal thickening. To insure the safety, long-term follow-up of the patients is needed, and also topical forms of KFGs may resolve this problem.

Conclusion

With respect to the findings of this study, it can be concluded that palifermin can reduce the oral mucositis in children with ALL. The mitogenic effect of palifermin leads to tissue protection capacity, which in turn increases the thickness of mucosal epithelium.

Conflicts of Interest

There is no conflict of interest in relation to this study.

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