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ORIGINAL ARTICLE

Clinical effectiveness of palifermin in prevention and treatment of oral mucositis in children with acute lymphoblastic leukaemia: a case–control study

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The aim of this study was to evaluate the efficacy of palifermin, an N-terminal truncated version of endogenous keratinocyte growth factor, in the control of oral mucositis during antiblastic therapy. Twenty patients undergoing allogeneic stem-cell transplantation for acute lymphoblastic leukaemia were treated with palifermin, and compared to a control group with the same number of subjects and similar inclusion criteria. Statistical analysis were performed to compare the outcomes in the treatment *vs.* control groups. In the treatment group, we found a statistically significant reduction in the duration of parenteral nutrition ($P=0.002$), duration of mucositis ($P=0.003$) and the average grade of mucositis ($P=0.03$). The statistical analysis showed that the drug was able to decrease the severity of mucositis. These data, although preliminary, suggest that palifermin could be a valid therapeutic adjuvant to improve the quality of life of patients suffering from leukaemia.
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INTRODUCTION

Treatment of acute lymphoblastic leukaemia may present several side effects.[1–3] During the conditioning regimen for haematopoietic stem cell transplantation (which includes total body irradiation or high-dose chemotherapy), and immediately after the transplant, patients may present a variety of symptoms, one of the most frequent and debilitating[4–6] of which is oral mucositis. The armamentarium for the management of oral mucositis consists of prophylactic and therapeutic measures, including topically and systemically applied non-pharmacological agents, as well as pharmacotherapeutics.[7–11]

Up to 80% of paediatric patients with haematological malignancies undergoing chemotherapy experience some degree of mucositis. Moreover, it appears that the prevalence of mucositis in paediatric patients is even greater than that in adults, most likely due to the more rapid cell division in this patient population.[12]

Endogenous keratinocyte growth factor (KGF) is a 28-kD heparin-binding member of the family of fibroblast growth factors (FGF-7) that was originally isolated from pulmonary fibroblasts as a protein with keratinocyte-stimulating activity.[13] KGF stimulates the growth of epithelial cells in an extended variety of tissues, but with no direct effect on other cell types. The specificity of KGF is due to the restricted expression of KGF receptor. KGF is produced by mesenchymal cells located adjacent to the epithelium of several organs such as the epidermis, oral and lower gastrointestinal epithelium, pancreas, liver, lung, urothelium, prostate epithelium and other tissues. KGF is produced by dermal fibroblasts within the skin and by lamina propria cells of the intestines.[14]

Epithelial cells express KGF receptor in many tissues including the epidermis, pancreas, liver, lung and urothelium.[15]

In this study, we evaluate the safety and efficacy of palifermin (Kepivance), a recombinant N-terminal truncated version of endogenous KGF with biological activity similar to that of the native protein, but with increased stability. Palifermin binds the KGF receptor, stimulating cell growth, proliferation, differentiation, and upregulation of cytoprotective mechanisms. Thus, palifermin may prevent the onset of epithelial cell apoptosis and prevent damage to the epithelial DNA, reduce the number of pro-inflammatory cytokines and increase protective enzymes against free radicals.[16]

Palifermin has been acknowledged as a drug that is able to decrease the incidence and duration of mucositis in patients with blood cancer who receive myelotoxic chemotherapy before undergoing bone marrow stem cell transplantation.[15–17]

Few studies have been performed on the efficacy of palifermin performed in paediatric patients.[18–19] In this context, the aim of this work is to report new data from a paediatric cohort. We present an interventional, case–control study in which palifermin is administered only to the study group, and its effects are compared with a control group that has not been administered the drug.[20–23]

MATERIALS AND METHODS

From April 2010 to April 2012, we analysed data from 20 patients treated with palifermin and who were enrolled in the conditioning regimen for an allogeneic transplant of blood-borne stem cells. The

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treatment group was compared to a control group of 20 subjects, with the same inclusion criteria, but who were treated with Benzydamine hydrochloride.[24–27]

Inclusion criteria:

- age less than 16 years;
- diagnosis of acute lymphoblastic leukaemia;
- potential allogeneic haematopoietic stem cell transplant recipient;
- scheduled to receive a myeloablative preparative regimen (cyclophosphamide/total body irradiation-based) prior to the infusion of the allogeneic graft;
- cardiac shortening fraction greater than or equal to 25%;
- serum creatinine less than twice the upper limit of normal for age;
- bilirubin less than 3.0 $mg \cdot dL^{-1}$;
- aspartate transaminase less than 500 $IU \cdot mL^{-1}$;
- alanine transaminase less than 500 $IU \cdot mL^{-1}$;
- amylase less than 1.5 times the upper limit of normal for age;
- lipase less than 1.5 times the upper limit of normal for age;
- no known hypersensitivity to *Escherichia coli*-derived proteins or palifermin;
- no active or recent (within 30 days prior to enrolment) gastrointestinal bleeding;
- no active or recent (within 30 days prior to enrolment) oral ulcerations;
- no active fungal infection, bacteraemia or viremia within 2 weeks prior to enrolment.

Exclusion criteria:

- pregnant or lactating (negative serum or urine pregnancy test within 14 days prior to enrolment).

All patients received radiotherapy in a dose of 12 Gy over eight sittings of 150 cGy twice a day for 4 days. The children involved in the study were between the ages of 7 and 16 years.

Palifermin was administered in a dosage of 60 $mg \cdot kg^{-1} \cdot d^{-1}$ as an intravenous bolus injection for three consecutive days before and three consecutive days after myeloablative therapy (for a total of six doses).

Each patient was evaluated daily for 30 days by the same oral pathologist. Every patient with mucositis was classified, in accordance with the grading proposed by the World Health Organization (WHO).[28]

Statistical analysis

We divided patients in three groups (I, II, III) based on the WHO's grading for oral mucositis. Group I included grades 1 to 4; group II includes grades 2, 3 and 4; and group III included grades 3 and 4.

For the analysis of the qualitative data, a *Z*-test[29] was used to compare the incidence of $a \geqslant 1$, $\geqslant 2$ and $\geqslant 3$ grade of mucositis between the study group and the control group. The manifestations of mucositis were classified into groups ($\geqslant 1$, $\geqslant 2$, $\geqslant 3$) without considering the various grading one by one. If a patient does not fall within group I, it indicates that the patient does not have any form of mucositis. The lower the frequency of group I, the greater the number of healthy patients (from the point of view of the oral affections) enrolled in the study. Accordingly, we studied the variation in the incidence of oral mucositis within the individual groups, and not the real effectiveness of Palifermin in the reduction of the grade of mucositis.

When the comparison was made between averages, and then between quantitative and not qualitative data, the Student's *t*-test.[29] In both the tests, the value of statistical significance was placed at $P \leqslant 0.05$.

RESULTS

In this study, patient characteristics such as age, gender, disease and disease status at the time of haematopoietic stem cell transplantation, donor status, stem-cell dose and radiotherapy dose were comparable between the two groups. Clinical data are illustrated in Table 1. An informed consent was obtained from the parents and/or guardians of all the patients for the purposes of accurate information and to ensure maximum collaboration.

Oral mucositis of grade $\geqslant 2$ (group II) was observed in 60% of participants (12 patients) in the group that was administered palifermin and in 86% of subjects in the control group (17 patients) ($P=0.032$) (Table 2). Mucositis of grade $\geqslant 3$ (group III) was observed in of 25% of participants (5 patients) in the study group, and in 55% (11 patients) in the control group ($P=0.154$), while mucositis of grade $\geqslant 1$ (hence, the manifestations of mucositis in totality of their clinical manifestations) had an incidence of 75% (15 patients) in the study group and 90% (18 patients) in the control group ($P=0.084$) (Table 2).

The average duration of the episodes of oral mucositis was 6 days when palifermin was administered (study group) and 12 days in the control group ($P=0.003$), as shown in Table 3. In addition, a significant difference was found in the average severity of mucositis, with a mean grading (according to the WHO classification) of 1.73 in treatment group and 2.47 in the control group ($P=0.03$) (Table 2). Moreover, thanks to a reduction in mucositis severity, the duration of parenteral nutrition was significantly reduced as well: 15 days in the treatment *vs.* 16 days in the control group ($P=0.002$) (Table 2). There was no difference in the number of documented opportunistic infections[30–32] (43% treatment group *vs.* 40% in the control group) and the

Table 1 Characteristics of patients included in the study group and the control group

Characteristics	Study group ($n=20$)	Control group ($n=20$)
Age/years		
Range	7–16	7–16
Median	11	11
Gender		
Female	9	10
Male	11	10
Post-transplant status of disease		
Complete remission	15	16
Partial remission	2	1
Chronic phase of disease	3	4
Dose of stem cells ($\times 10^6$ per kg of CD34*)	6.04	5.85

Table 2 Comparison between results obtained in the study group and the control group

Results	Study group	Control group	*P* value
Incidence of mucositis group I	15 (75%)	18 (90%)	0.084
Incidence of mucositis group II	12 (60%)	17 (86%)	0.032
Incidence of mucositis group III	3 (25%)	11 (55%)	0.154
Duration of parenteral nutrition (mean)	16 (0–32)	26 (13–40)	0.002
Duration of manifestation of mucositis (mean)	6 (0–19)	12 (0–30)	0.003
Grading of mucositis	1.73	2.47	0.030

Table 3 Mucositis temporal distribution in all patients

Study group	Days of mucositis	Control group	Days of mucositis
1	6	1	12
2	4	2	14
3	5	3	15
4	7	4	12
5	8	5	10
6	8	6	9
7	7	7	12
8	5	8	13
9	4	9	14
10	6	10	12
11	9	11	11
12	7	12	10
13	6	13	12
14	4	14	15
15	5	15	9
16	4	16	10
17	7	17	14
18	8	18	12
19	6	19	14
20	5	20	10

Table 4 Secondary events to the administration of palifermin

Side effects	Study group percentage (number)	Control group percentage
Rash	30% (6)	—
Erythema	30% (6)	—
Altered taste	10% (2)	—
Pain of the buccal and tongue mucosa	10% (2)	—

100-day survival rate was also very similar in both groups: one patient in the treatment group and two patients in the control group died before the 100th day after allergenic haematopoietic stem cell transplantation.

In summary, our data indicate that Palifermin may be most successful in reducing the incidence of mucositis in subjects categorized as group 2 (P=0.032) and also in reducing the overall duration and severity of mucositis.

Observed adverse effects included skin rash, skin erythema and altered taste; two patients in the treatment group, in particular, experienced severe pain in the tongue, buccal mucosa and palate, measured as a value of 7 on the Visual Analogue Scale (Table 4).

DISCUSSION

This preliminary study seems to confirm the clinical efficacy of the Palifermin in the treatment of mucositis in paediatric patients.[15,17]

Parameters of comparison between the study group and the control group such as the mean duration of parenteral nutrition and the mean duration of mucositis were also reduced by administration of the drug. In addition, subjects receiving Palifermin also experienced less severe mucositis compared to the controls. Moreover, the incidence of mucositis in groups I, II and III was always lower in the treatment group compared to the control group. Although not statistically significant in groups 1 and 3, the trend observed in this study appears to indicate that Palifermin is likely to be beneficial in the reduction of mucositis overall (Figure 1). A larger study is needed verify this benefit. Mucositis is one of the most debilitating and expensive side effects

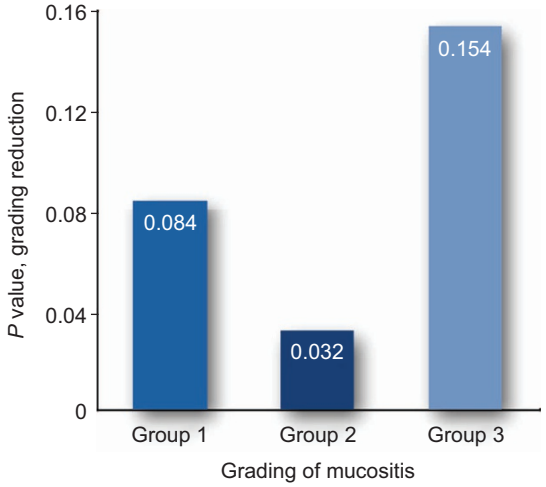

Figure 1 ***P*** **value, incidence of grading reduction in the different groups.**

to treat, and any reduction in its incidence, duration or severity is welcomed.

These observations could be directly related to the mechanism of action of palifermin,[15,17] that, as we observed, operates at the level of the mucosa and not at the level of the pathogenetic mechanisms of the disease.

Moreover, the comparison between the treatment and control groups, shows that the drug drastically reduces the use of parenteral nutrition and the duration of the manifestations of mucositis itself. These findings allow us to conclude that palifermin, while not guaranteeing to eliminate mucositis, allows a remarkable improvement in the patient's condition, which is critical for individuals who are already highly debilitated by leukaemia and chemoradiotherapies. Moreover, the administration of palifermin could be considered generally safe and without significant complications.

In conclusion, palifermin cannot be recommended as a cure for mucositis (of any grade) with 'statistical certainty' due to the variability in the two groups.

We believe that through a multimodal approach of appropriate oral cavity care, i.e., with proper odontostomatological management[31–32] application of prevention protocols,[33] oral infection control[34] and monitoring oral health,[35] it is possible to improve the quality of life of children with leukaemia before, during and after systemic therapy.

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