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ORIGINAL ARTICLE

Effectiveness of palifermin in the prevention of oral mucositis in patients with haematological cancers

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KEYWORDS
Mucositis;
Keratinocyte growth factor (KGF);
Palifermin;
Prevention;
Chemotherapy;
Haematological cancers;
Stem cell transplantation

Abstract
Objective: To assess the effectiveness of palifermin for the prevention of oral mucositis in patients with haematological cancers.
Method: Retrospective observational study of cohorts of patients with haematological cancer undergoing cytotoxic therapy causing hematopoietic ablation.
The main variable assessed was the duration of the oral mucositis. Secondary variables assessed were incidence of mucositis, febrile or septic neutropenia and the administration of opioids and parenteral nutrition.
Results: We included 36 patients in this study, 11 in the group that received palifermin and 25 in the control group. The duration of oral mucositis was 4.6±3.1 days (median: 5 days) in the patients treated with palifermin in comparison with 7.4±4.0 days (median: 6 days) in patients treated with conventional prophylactic therapy ($P<.05$). However, no significant differences were seen in the incidence of mucositis, febrile or septic neutropenia, opioid administration of the use of parenteral nutrition.
Conclusions: Prophylactic treatment with palifermin reduces the duration of oral mucosities in patients with haematological cancer. Further studies are necessary with larger samples to be able to assess palifermin and its influence on other variables, such as incidence of mucositis, sepsis, febrile neutropenia, etc.

PALABRAS CLAVE
Mucositis;
Factor estimulante de queratinocitos;
Palifermina;

Efectividad de la palifermina en la prevención de la mucositis oral en pacientes oncohematológicos

Resumen
Objetivo: Evaluar la efectividad de la palifermina en la prevención de la mucositis oral (MO) en pacientes oncohematológicos.

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Prevención;
Quimioterapia;
Neoplasias hematológicas;
Trasplante de células madre

Método: Estudio observacional retrospectivo de cohortes en pacientes con neoplasias hematológicas, sometidos a tratamiento mieloablativo de acondicionamiento y posterior trasplante autólogo de progenitores hematopoyéticos, y que reciben como profilaxis de la mucositis palifermina u otro tratamiento convencional. La variable principal evaluada fue la duración de la MO. Las variables secundarias fueron la incidencia de mucositis, neutropenia febril o sepsis y la administración de opiáceos o nutrición parenteral.

Resultados: Se incluyeron 36 pacientes en el estudio, 11 en el grupo de palifermina y 25 en el grupo control. La duración de la MO fue de 4,6 ± 3,1 días (mediana: 5 días) en los pacientes tratados con palifermina respecto a 7,4 ± 4,0 días (mediana: 6 días) en los tratados con profilaxis convencional ($p < 0,05$). A pesar de todo, no se observaron diferencias significativas en la incidencia de mucositis, sepsis o neutropenia febril, la administración de opiáceos o la utilización de nutrición parenteral.

Conclusiones: El tratamiento profiláctico con palifermina permite reducir la duración de la MO en pacientes oncohematológicos. Se necesitan más estudios y con un tamaño muestral mayor para poder evaluar el papel de la palifermina sobre otras variables, tales como la incidencia de la mucositis, sepsis, neutropenia febril, etc.

Introduction

The treatment of solid malignant tumours and leukaemias with cytotoxic chemotherapy or radiation therapy is becoming increasingly effective. However, significant adverse effects in the short and long-term are still associated.[1] These adverse effects, caused by the treatments administered, are among others, disorders which affect the functioning and the integrity of the oral mucosa that result in an inflammatory and ulcerative process called oral mucositis (OM).[2]

OM, in addition to causing discomfort and pain, can lead to difficulty in oral nutrition, a delay in the administration of oral drugs, prolonged hospitalisation and, in some cases potentially life-threatening infections.[1,3-6]

Furthermore, severe MO can cause unscheduled decreased doses of chemotherapy and radiation therapy, and can even lead to the suspension of treatment, which affects the efficacy of the therapy and reduces the life expectancy of the patients. An increased risk was observed in both mortality at 100 days and mortality related to treatment post-autologous stem cell transplantation.[3]

Furthermore, from a patient's perspective, OM is often regarded as one of the most debilitating complications that cause a significant decline in the quality of life of the patients.[1,7-10]

There are several scales commonly used to assess and quantify the severity of mucositis, including the scale established by the WHO which has determined five levels of severity (from 0-4) with Grade 3 and 4 being the most debilitating[11] (Table 1).

There was no specific prophylactic treatment available for mucositis[12,13] until palifermin was launched on the market. Instead, a wide variety of treatments were used, such as, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), sucralfate, glutamine, lidocaine chlorhexidine, nystatin and amifostine, as well as laser treatments and cryotherapy, among others. Many of these treatments were intended to alleviate symptoms. However, the outcomes achieved, in terms of efficacy, were inconclusive and even contradictory.[14]

Palifermin is a human recombinant keratinocyte growth factor, obtained through recombinant DNA technology. It binds to specific receptors on the surface of epithelial cells and stimulates the proliferation, differentiation and upregulation of cytoprotective mechanism.[15,16] Drug approval by the EMEA and the AEMPS (Spanish Agency of Medicines and Health Products), to reduce the incidence, duration and severity of OM, is based on a Phase III randomised, double-blind, controlled pivotal study[7] to evaluate the efficacy of palifermin in the prevention of OM, in patients with haematological cancers undergoing cytotoxic therapy causing haematopoietic ablation with total body irradiation and high doses of chemotherapy (CT) (based on treatment regimens with etoposide and cyclophosphamide) following haematopoietic stem cell transplantation (HSCT). This myelotoxic regimen, which is standard treatment in the United States, is associated with a high incidence of severe OM (Grade 3 and 4 according to the WHO scale),[11] affecting 70%80%of patients.[6,10] However, it is not used routinely in Spain, where the standard practice is treatment regimens of high-dose chemotherapy without radiation therapy, such as the BEA regimen (busulfan, etoposide and cytarabine), BEAM (carmustine, etoposide, cytarabine and melphalan), CBV (carmustine, etoposide and cyclophosphamide) and high-dose melphalan, which are less mucotoxic and affect a smaller percentage of patients (30%-50%).[6,9,10] These differences in the use of different treatment regimens and the utilisation criteria causes the outcomes on efficacy, published in the bibliography, to be unsuitable in our setting.[17]

Table 1 The World Health Organization Toxicity Scale for grading oral mucositis[16]

Degree	*Symptoms*
0	No symptoms
1	Irritation with or without erythema
2	Erythema and ulcers; can eat solid foods
3	Extensive erythema with ulcers; requires liquid diet only
4	Mucositis that prevents oral intake (solids and liquids)

Within this context, the *purpose* of this study is to evaluate the efficacy of palifermin in the prevention of OM in patients with haematological cancers undergoing high-dose chemotherapy and autologous stem cell transplantation, versus patients receiving other conventional preventive treatments.

Method

A retrospective observational analysis was conducted between January 2004 until February 2009 on cohorts of patients with a diagnosis of haematological cancer treated with high doses of chemotherapy as myeloablative conditioning and subsequent autologous haematopoietic stem cell transplantation, received palifermin as either a prophylactic measure or in the treatment of OM versus another conventional prophylactic treatment.

The identification of patients included in the study was carried out through the IDC-9-CM system using the hospital's MBDS. The demographic data and relevant variables were obtained through reviewing the medical records for which a data collection sheet was designed (Figure).

The primary variable for efficacy was the median duration of OM regardless of the grade. Secondary variables measured the overall incidence of mucositis, the grade and severity of mucositis, the need to administrate opioid analgesia, the need for parenteral nutrition and the incidence of febrile neutropenia and sepsis. Parenteral nutrition was only recorded when the indication was the inability to achieve proper food intake per oral route due to mucositis. Furthermore, the administration of opioid analgesics was only admitted to control pain secondary to mucositis.

Mucositis classification by grade of severity was performed by the attending physician based on the WHO scale.[11]

The simple size was calculated based on the efficacy endpoints from the primary efficacy variable in the Phase III clinical pivotal study that was used for approval of the indication.[7] To achieve a potency of 80% and to detect differences in the null hypothesis test, using the bilateral Student's *t* test for two independent samples, taking into account that the significance level is 5%, and assuming that, in the clinical trial, the mean duration of severe mucositis (Grade 3-4) in the control group is 10.4 days while the mean duration in the experimental group is 3.7 days and the standard deviation of both groups is 5.2 days, the study would have to include 23 patients where 14 patients would be in the control group (patients treated with conventional treatment) and 9 patients in the experimental group (patients treated with palifermin).

Processing and statistical analysis was performed using the SPSS® statistics software for Windows Version 12.0. The descriptive statistics of the quantitative variables was performed using measures of central tendency (mean and median) and dispersion (standard deviation). The normal distribution of the primary variables was evaluated using the Kolmogorov-Smirnov test. The comparison between the quantitative variables was performed using the Student's *t* test for independent samples and the χ^2 test for the categorical variables.

Results

The study included all 36 patients with a diagnosis of haematological cancer undergoing high doses of CT as myeloablative conditioning and subsequent HSCT. The experimental group was made up of 11 patients who received palifermin as a preventive treatment for OM according to the dose and guidelines for administration that were specified in the Technical Data Sheet.[15] The control group was made up of 25 patients who received conventional prophylactic treatment through the administration of a mouthwash containing 2% mepivacaine, dexamethasone and 0.05% chlorhexidine. All patients received general care for proper oral hygiene and rinsing with an antiseptic solution. Table 2 shows the baseline characteristics for each patient included in the study.

The median duration of OM was 5 days (interval: 0-9 days) in patients treated with palifermin compared to 6 days (interval: 0-18 days) in those patients treated with conventional prophylaxis. The mean duration of OM was, significantly longer in the control group than in the experimental group (7.4±3.9 days versus 4.6±3.1 days, $P<.05$).

The overall incidence of OM was 82% in the group treated with palifermin and 96% in the control group. No significant differences were detected in the overall incidence of mucositis ($P=.16$). However, a favourable trend was observed in the group treated with palifermin (9/11 patients versus 24/25 patients in the control group). There were no cases whatsoever of Grade 3-4 mucositis observed in the group treated with palifermin. The incidence in the control group was 4/25 patients for Grade 3 mucositis, with a median duration of 10.5 days, and 3/25 patients for Grade 4 mucositis with a median duration of 15 days. The median duration of Grade 3 and 4 OM in this group was 12 days.

The need for parenteral nutrition was correlated with the incidence and severity of the mucositis since no patient treated with palifermin needed parenteral nutritional support. However, 4/25 patients treated with conventional prophylactic therapy did, indeed, receive parenteral nutritional support.

Opioid analgesics were administered to nearly half the patients treated with palifermin, (5/11 patients) and to a smaller number in the group treated with conventional prophylactic therapy (8/25 patients).

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HOJA DE RECOGIDA DE DATOS

Pacientes sometidos a tratamiento mieloablativo y trasplante autólogo de progenitores hematopoyeticos

NCH:	**Diagnóstico**

Datos antropométricos		
Fecha de nacimiento:	**Edad:**	**Sexo:**
Peso (kg):	**Talla (cm):**	**SC (m^2)**

Esquema de quimioterapia previo	***Fecha inicio/Fecha fin***
1.-	
2.-	
3.-	

Esquema mioloablativo de acondicionamiento para TPH	
ESQUEMA (Dosis: mg)	**Inicio: ____ /____ /____ Fin: ____ /____ /____**

Profiláxis mucositis: Palifermina ❑ Sí ❑ No Tto. convencional _____	
Pre-aconcicionamiento (60 mcg/kg/d x dosis consecutivas 3a 24-48 preQT	**Inicio: ____ /____ /____ Fin: ____ /____ /____**
Post-transplante ((60 mcg/kg/d x dosis días 0, 1, 2.)	**Inicio: ____ /____ /____ Fin: ____ /____ /____**

Efectos adversos a palifermin: ❑ **Fiebre** ❑ **Prurito** ❑ **Artralgia** ❑ **Edema** ❑ **Dolor perioral** ❑ **alteración del gusto** ❑ ***Rash*** ❑ **Hipertrofia mucosa lingual** ❑ **Parestesia** ❑ **Otros**

Mucositis ❑ Sí ❑ No	**Grado*:**	

*Escala WHO (World Health Organization: 0: Sín síntomas, I: Escozor con o sin eritema, II: Eritema y ulceraciones, capacidad de ingesta de sólidos, III: Eritema extenso con ulceraciones, incapacidad de ingesta de sólidos, IV: incapacidad ingesta oral).

Tratamiento	**Posología/Vía adm.**	**Fecha inicio**	**Fecha fin**
Sintomático			
Anagelsia opioide			
Nutrición parenteral	**Macro/Micronutrientes**	**Electrolitos (mEq)**	**Fecha inicio /Fecha fin**

Figure Data collection sheet for patients with haematological cancers undergoing myeloablative treatment and autologous stem cell transplant treatment. CT indicates chemotherapy; HSCT, haematopoietic stem cell transplantation.

Table 2 Baseline characteristics of the patient population included in the study in both groups

Characteristics	*Palifermin-treated group (n=11)*	*Conventional prophylactic-treated group (n=25)*
Sex, females/males	4/7 (36%/64%)	7/18 (28%/72%)
Age, years		
Median	53	56
Interval (min-max)	(29-70)	(18-70)
Diagnosis		
AML	1/11 (9%)	1/25 (4%)
HODGKIN'S DISEASE	2/11 (18%)	7/25 (28%)
MM	8/11 (73%)	12/25 (48%)
NHL	–	3/25 (12%)
CLL	–	2/25 (8%)
Conditioning chemotherapy		
BEA	1 (9%)	1 (4%)
BEAM	–	5 (20%)
CBV	2 (18%)	6 (24%)
MELFALAN	8 (73%)	12 (48%)
Cyclophosphamide+ICT	–	1 (4%)

AML indicates acute myeloid leukaemia; BEA, busulfan, etoposide, cytarabine; BEAM, carmustine, etoposide, cytarabine and melphalan; CBV, carmustine, etoposide, cyclophosphamide; CLL, chronic lymphocytic leukaemia; ICT, total body irradiation; MM: multiple myeloma; NHL, non Hodgkin's lymphoma.

Table 3 Results of the primary variable of the study and the secondary variables

Variables	*Palifermin-treated group (n=11)*	*Conventional prophylactic-treated group (n=25)*
Primary variable		
Duration of any grade of OM, days		
Mean±SD	4.6±3.1*	7.4±3.9*
Median (min-max)	5 (0-9)	6 (0-18)
Secondary variables		
Overall Incidence of OM	9/11 (82%)	24/25 (96%)
Incidence of OM by severity:		
Grade 0 incidences	2/11 (18%)	1/25 (4%)
Grade 1 incidences	5/11 (46%)	8/25 (32%)
Grade 2 incidences	4/11 (36%)	9/25 (36%)
Grade 3 incidences	0/11 (0%)	4/25 (16%)
Grade 4 incidences	0/11 (0%)	3/25 (12%)
Need for TPN	0/11 (0%)	4/25 (16%)
Need for opioid analgesic treatment	5/11 (45%)	8/25 (32%)
Incidences of febrile neutropenia	2/11 (18%)	5/25 (20%)
Incidences of sepsis	3/11 (27%)	3/25 (12%)

OM indicates oral mucositis; SD, standard deviation; TPN, total parenteral nutrition.
*$P<.05$ grading according to the WHO toxicity scale.[11]

The incidence of febrile neutropenia was higher in the control group, 5/25 patients versus 2/11 patients, whereas the opposite occurred in the palifermin-treated group in terms of the incidence of sepsis, 3/22 patients versus 3/11 patients.

Table 3 shows the results of the primary variable and the secondary variables.

Six patients presented ten adverse effects from the administration of palifermin. Three patients experienced lingual thickening and hypertrophy of the buccal mucosa, 2

presented with oedema or erythema of the face and perioral area, 2 reported alterations in taste and 2 dermal toxicity and one patient had severe skin toxicity with severe exanthema on the face and perioral area. However, all patients completed their treatment with palifermin.

Discussion

To date, all available data in terms of the efficacy of the different treatments prescribed to prevent and treat mucositis are heterogeneous and inconclusive.[8] At present, several clinical guidelines include among their recommendations, prophylactic treatment with palifermin to reduce the incidence and duration of mucositis in patients with haematological cancer who underwent HSCT and prior myeloablative treatment.[18-20] This last treatment is only recommended when it includes a high dose of CT and total body irradiation,[17] and cryotherapy is recommended as a prophylaxis of MO when myeloablative treatment includes high doses of melphalan,[19] as occurs in 56% (20/36) of the patients in this study. However, there is no data available on head-to-head clinical studies comparing cryotherapy and palifermin.

Spielberger R et al associate the use of palifermin with a reduction in the duration of mucositis.[7] Palifermin reduced the duration of mucositis in 6 and 3 days, respectively, for mucositis and severe mucositis. However, no palifermin-treated patient experienced severe mucositis (Grade 3 and 4), which is the most disabling for the patient. Nonetheless, this could be due to less mucotoxicity in the conditioning regimens which do not include radiation therapy.

Severe mucositis has been associated with difficulty in swallowing and the inability to take food by mouth.[9] Therefore, the need to initiate parenteral nutrition in order to prevent malnutrition in these patients could be used as a secondary efficacy variable for palifermin. It is evident that for a correct evaluation of this variable, the need for nutritional support due to other common causes must be taken into consideration such as gastrointestinal toxicity and prior states of malnutrition, as well as the different medical criteria for initiating this treatment.

As to the need for opioid analgesics, the results are not favourable for treatment with palifermin, which suggests that despite ruling out the need for analgesia due to other causes, in six patients with Grade 1 and 2 mucositis, opioid analgesics co-exist with other adverse effects due to palifermin's mechanism of action that, in part, affect the skin and the oral epithelium.[15,16] This could be an important confusing variable for both the grading of mucositis and for the indication of opioid analgesic treatment. However, to provide solid evidence of the relationship between the need for opioid treatment and the severity of mucositis, the total cumulative dose and treatment duration must be taken into consideration.[5]

Unlike the test conducted by Spielberger et al,[7] the variation in the post-transplant hospitalisation days was not taken into consideration since it is a variable whose results could be misleading, since it can be affected by various factors, including complications associated with patient's myelosuppressive status, toxicity resulting from the intensification of chemotherapy for pre-transplant conditioning such as liver toxicity, renal toxicity, etc.

The outcomes of this study contrast with those recently presented by Romero et al,[20] where the utilisation of palifermin did not reduce the incidence of Grade 3-4 mucositis, although there is a trend that can be seen in the reduction of the overall incidence of mucositis. This study, like ours, presents a very small sample size which limits the precision and statistical power of the findings. Although the number of patients included in the study was higher than the previous estimate for the sample size, this calculation was performed using the mean duration of severe mucositis as the efficacy variable, which did not occur in any patient whatsoever in the palifermin-treated group. Using the duration of mucositis as an efficacy variable, the statistical power obtained would be 57%, which is less than the 80% desired in these types of studies.

However, among the major limitations of the study, is the use of different conditioning regimens and their degree of impact in the onset of mucositis as this could be a source of confusion when evaluating the results and the retrospective collection of data used in the analysis, which prevent or hinder their verification. Furthermore, the perception of mucositis may differ between the patient and the physician since the evaluation tools (scales) are based solely on observation and assessment of the severity of the clinical picture regardless of the patient's perspective. Mucositis, even in its milder forms, is a serious complication that can lead to inadequate treatment of symptoms and inaccurate conclusions about the efficacy of the treatment utilised. Hence, the use of instruments based on patient self-assessment compared to the clinical scales would be of great help in determining the severity of mucositis in a more precise manner.[9]

To conclude, prophylactic therapy with palifermin shortens the duration of OM in patients with haematological cancers undergoing myeloablative treatment with high doses of CT that require autologous haematopoietic stem cell treatment. However, the high cost of palifermin and the efficacy endpoints published make it advisable to conduct studies with a larger sample size to establish the impact of palifermin on other variables, such as the incidence of mucositis, sepsis, febrile neutropenia and pharmacoeconomic studies[21,22] to facilitate the decision-making process for selecting an effective prophylactic treatment to prevent mucositis resulting from myelotoxic regimens utilised in our clinical practice.

Conflict of interest

The authors affirm that they have no conflict of interest.

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