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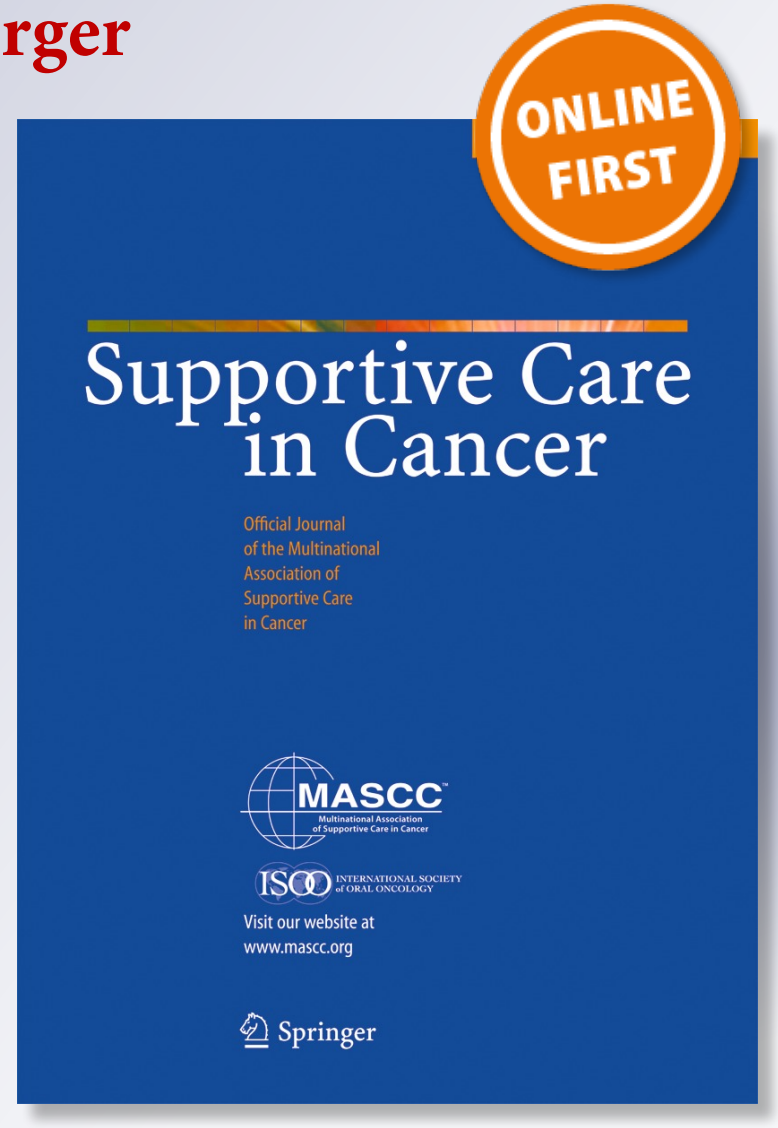

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ORIGINAL ARTICLE

Palifermin for prevention of oral mucositis in allogeneic hematopoietic stem cell transplantation: a single-institution retrospective evaluation

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Abstract
Purpose The purpose of this study is to assess the impact of palifermin on oral mucositis (OM) and its sequelae in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) who were conditioned with fractionated total body irradiation (FTBI) and etoposide.
Methods This retrospective chart review study compared the effect of palifermin on the development of OM in patients who received this agent during an allo-HSCT (n=99) to those who did not (n=30). The primary end points were severity and duration of OM. Secondary end points included requirements for opioids, total parenteral nutrition (TPN), and intensive oral care; incidence of infection; length of hospital stay; and overall survival.
Results There was no significant difference in the incidence of all grades of OM, but incidence of severe OM was decreased in palifermin-exposed patients (34 vs 80 %, p<0.0001). In patients who developed OM (all grades), the median duration of OM was shorter in palifermin-exposed patients (13 vs 18 days, p=0.0001); there was no difference in the median duration of severe OM. Patients who received palifermin used less opioids and required a shorter duration of intensive oral care. There was no difference in duration of TPN, incidence of infection, length of hospital stay, and overall survival.
Conclusions Our findings demonstrated a significant benefit with the use of palifermin for allo-HSCT recipients who were conditioned with FTBI and etoposide. Palifermin can potentially improve quality of life for this patient population and reduce complications and resources used during the transplant process. A randomized clinical trial is required to confirm these results.

Keywords Allogeneic stem cell transplant · Fractionated total body irradiation · Mucositis · Palifermin · Retrospective

Introduction

Hematopoietic stem cell transplantation (HSCT), which often includes high-dose chemotherapy and radiation as part of conditioning, is a well-established treatment for hematologic malignancies. Oral mucositis (OM) is a frequent complication of this treatment modality and requires intervention in approximately 70–80 % of patients receiving radiation-based conditioning regimens [1–3]. The incidence and severity of OM is known to vary by conditioning regimen, prior history of mucositis, individual patient variability, and oral status prior to treatment [2, 4–6].

Oral mucositis can result in significant morbidity, including oral ulceration, dysphagia, pain requiring treatment with intravenous (IV) opioids, anorexia necessitating parenteral nutrition, and infections from translocated bacteria that transverse

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the impaired mucosal barrier [2, 7]. Occasionally, severe OM may be associated with significant mucosal bleeding, tissue inflammation, and edema that may require endotracheal intubation to protect a compromised airway [1]. The severity of OM among patients undergoing HSCT directly correlates with the duration of febrile neutropenia, narcotic usage, and hospitalization [8].

Despite these findings, research on prevention and management strategies of OM has lagged behind research in other cancer-treatment-related morbidities like nausea, vomiting, and cytopenia. This disparity is likely related to complex risk assessment, confounding treatment factors, and different techniques of rating OM. Due to few advances in the treatment of OM, supportive care and symptom palliation are the foundation of OM management.

Keratinocyte growth factor (KGF) is a member of the fibroblast growth factor family with epithelial cell proliferative properties [9]. Palifermin (Kepivance®), a recombinant human KGF, affects fibroblasts and specifically stimulates the growth and antiapoptotic potential of epithelial cells that express the KGF receptor without affecting nonepithelial cells that lack the receptor [10]. Palifermin has been found to reduce chemotherapy- and radiation-induced injury to the mucosal lining of the oral cavity and the lower gastrointestinal tract in animal models [10, 11]. In particular, it induces cell growth, differentiation, and thickening of the epithelial tissues, thereby providing cytoprotective effects throughout the gastrointestinal epithelia [10, 12]. In 2004, palifermin was approved in the USA for OM prevention in patients with hematologic malignancies who receive myelotoxic therapy that requires hematopoietic stem cell support. The approval was based on a multi-center, double-blind, placebo-controlled, randomized trial in 212 patients who received an autologous HSCT (auto-HSCT) with total-body irradiation (TBI), etoposide, and cyclophosphamide conditioning. This trial and additional follow-up studies have found that palifermin decreases the incidence and duration of severe OM, as well as the use of opioid analgesics and total parenteral nutrition (TPN) [13, 14].

Systematic reviews and guidelines support recommendations for use of palifermin to prevent OM in patients who receive auto-HSCT with TBI conditioning [5]. However, there is limited published experience with palifermin in the context of allogeneic HSCT (allo-HSCT). To explore the impact of palifermin in allo-HSCT among patients conditioned with fractionated total body irradiation (FTBI) and etoposide, a regimen associated with high incidence of OM, we conducted a retrospective chart review study to evaluate possible differences between severity/duration of OM and other clinical end points previously found to be associated with OM in patients who received palifermin compared to those who did not.

Methods

Patients

Patients with hematologic malignancies, ≥18 years of age, conditioned with FTBI and etoposide as part of an allo-HSCT using hematopoietic stem cells from a matched related or unrelated donor which occurred between January 2005 and December 2009 at City of Hope (COH) were eligible. A consecutive case series of 30 patients who underwent allo-HSCT between January 2005 and December 2005 were identified for inclusion in the control group. Ninety-nine consecutive patients who received an allo-HSCT between December 2006 and December 2009, after palifermin was officially added as a component of FTBI-based conditioning regimens at COH, were identified for inclusion in the palifermin group. The January 2005 study start date for patient inclusion was selected to ensure consistency in supportive care practices across the two groups. Similarly, the December 2005 end date for the control group was selected given that shortly after this date, palifermin became the standard of care for OM prevention for radiation-based conditioning regimens at COH. Changes in the hospital's standard of care during these time periods were minor and would not have contributed to differences between the groups.

Treatment

Conditioning therapy and supportive care were administered according to the COH allo-HSCT standard operating procedures. For patients treated with a tacrolimus- and sirolimus-based graft-versus-host disease (GVHD) prophylaxis regimen, FTBI was delivered in 11 fractions over 4 days (day −8 to day −5, 1320 cGy total) before chemotherapy was administered. Chemotherapy included IV etoposide (60 mg/kg) administered the day after the last radiation fraction (day −4). Stem cells were infused on day 0. Patients who received a tacrolimus- or cyclosporine and methotrexate (MTX)-based GVHD prophylaxis regimen received the same conditioning regimen, but the regimen started 1 day later (e.g., FTBI started on day −7). All patients received viral and fungal prophylaxis according to COH allo-HSCT standard operating procedures.

Patients in the palifermin group received IV palifermin (60 mcg/kg/day) for 3 consecutive days, with the third dose given 24 h before the initiation of FTBI. Patients received three additional doses of palifermin after completion of the conditioning regimen, starting on day 0 until day +2.

All patients with expected or existing OM after allo-HSCT received a comprehensive oral care treatment regimen called Critical Oral Hygiene for Treatment of Edematous Aggressive Mucositis (C.O.H. T.E.A.M.) administered by certified respiratory therapists who documented mucositis assessments every 3 days; OM duration and grade were collected through the forms that were completed during the assessments. Control

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and palifermin group patients (96.7 % (29 of 30) and 84.8 % (84 of 99), respectively) received C.O.H. T.E.A.M. For patients who did not receive C.O.H. T.E.A.M., OM duration and grade were collected through review of daily physician and nursing notes. Oral mucositis grade was by the four-grade National Cancer Institute Common Toxicity Criteria (Version 2.0) (NCI CTCv2.0). For the purposes of this study, OM grades 1 and 2 were categorized as "mild" and grades 3 and 4 were categorized as "severe" (Table 1).

The use of C.O.H. T.E.A.M., opioids, and TPN, as well as the incidence of blood infections, was assessed after allo-HSCT until discharge or death. Information concerning TPN and opioid use was obtained from the pharmacy computer system. Opioid use was calculated as the sum of IV morphine equivalents for scheduled and as needed oral, intravenous, and transdermal opioids as well as patient-controlled analgesia (PCA). Patients' progress notes were reviewed to ensure that the PCA was initiated for pain related to OM. Presence of bacteremia, fungemia, and viremia was assessed from the start of conditioning until day +100. Incidence of bacteremia and fungemia was assessed by blood cultures, cytomegalovirus (CMV) was assessed by blood cultures and/or polymerase chain reaction (PCR), and viremia was assessed by PCR. Length of hospital stay was defined as the duration from the date of admission until discharge or death.

The COH Institutional Review Board (IRB) approved the retrospective analysis of these data.

Statistical analysis

The primary study end points for evaluation were the incidence and duration of overall and severe OM. Secondary end points included duration of C.O.H. T.E.A.M., PCA, and TPN use; quantity of opioid use; incidence of bacteremia, fungemia, and viremia; length of hospital stay; and overall survival (OS). Medians and ranges were compared using the Wilcoxon rank-sum test. Fisher's exact test was used on the contingency tables. A backwards-elimination logistic regression model was used to evaluate the impact of select factors on the outcome of severe OM. Survival estimates were calculated based on the Kaplan-Meier product-limit method, and 95 % confidence intervals were calculated using the logit transformation and the Greenwood variance estimate. Differences between Kaplan-Meier curves were assessed by the log-rank test. Patients who were alive at the time of analysis were censored at the last contact date. Overall survival was measured from transplant to death from any cause. Statistical significance was set at the $p<0.05$ level; all p values were two-sided.

Results

Patient demographic, disease, and treatment characteristics are provided in Table 2. With the exception of patient age at allo-HSCT, patient characteristics were found to be similar between the two groups with respect to gender, diagnosis, disease status at transplant, donor type, source of stem cells, and GVHD prophylaxis regimen. The median age at transplant was higher in the palifermin group when compared to the control group (42.0 years [range 18.0–59.2] vs 34.3 years [range 18.5–56.7], $p=0.02$).

Oral mucositis (all grades) developed in 94 (95 %) patients in the palifermin group and in all 30 patients in the control group ($p=0.59$). Severe OM was seen in 34 (34 %) patients in the palifermin group and in 24 (80 %) patients in the control group ($p<0.0001$) (Fig. 1). As part of a backwards-elimination multivariable logistic regression model, these data showed that patients who received MTX as part of their GVHD prophylaxis regimen were more likely to develop severe OM, OR=3.21 (95 % confidence interval (CI) 1.38–7.46; $p=0.007$). Age at allo-HSCT, disease status, and source of stem cells were not found to impact the odds of developing OM.

In patients who developed OM (all grades), the median duration of OM was 13 days (range 1–35) in the palifermin group and 18 days (range 8–65) in the control group ($p=0.0001$); the median duration of severe OM was not found to be different between the two groups (5 days, $p=0.95$) (Fig. 2). Oral mucositis assessment was limited due to mechanical ventilation in two patients in the control group (one case related to severe OM) and five patients in the palifermin group (four cases related to severe OM).

Table 1 National Cancer Institute Common Toxicity Criteria Version 2.0 (NCI CTCv2.0) used to grade oral mucositis

Toxicity description	CTC grade	Modified COH grade
Painless ulcers, erythema, or mild soreness in the absence of lesions	1	Mild
Painful erythema, edema, or ulcers, but can swallow	2	
Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral/enteral nutritional support	3	Severe
Severe ulceration or requiring prophylactic intubation or resulting in documented aspiration pneumonia	4	

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Table 2 Patient demographic, disease, and treatment characteristics

Characteristic	Palifermin group (n=99) N (%) or median (range)	Control group (n=30) N (%) or median (range)	p value
Male gender	50 (51)	20 (67)	0.15
Age, years	42.0 (18.0–59.2)	34.3 (18.5–56.7)	0.02
Diagnosis			
ALL	59 (59.6)	18 (60)	0.34
AML	40 (40.4)	11 (36.7)	
LBL	0 (0)	1 (3.3)	
Disease status at transplant			
1 CR or untreated	58 (58.6)	15 (50)	0.41
More advanced disease	41 (41.4)	15 (50)	
Donor type			
Matched related	74 (74.7)	20 (66.7)	0.48
Matched unrelated	25 (25.3)	10 (33.3)	
Stem cell source			
Bone marrow	14 (14.1)	1 (3.3)	0.19
Peripheral stem cell	85 (85.9)	29 (96.7)	
GVHD prophylaxis regimen			
MTX-containing regimen	28 (28.3)	11 (36.7)	0.38
No MTX-containing regimen	71 (71.7)	19 (63.3)	

ALL acute lymphocytic leukemia, *AML* acute myeloid leukemia, *CR* complete remission, *LBL* lymphoblastic leukemia, *MTX* methotrexate

The median duration of comprehensive oral care with C.O.H. T.E.A.M. was shorter in the palifermin group (13 days, range 0 to 61) when compared to that in the control group (15 days, range 0 to 47; p=0.01). With respect to pain control, median duration of PCA use was less in the palifermin group when compared to the control group (14.5 days, range 0 to 49, vs 22.5 days, range 8 to 36 days; p=0.01). Similarly, palifermin was associated with reduced use of opioids as measured by the median cumulative dose of morphine equivalents administered (543 mg, range 0 to 10,277 mg, vs 900 mg, range 225 to 18,137 mg; p=0.02).

The median duration of TPN use was not significantly different between the palifermin and control group (25 days, range 0 to 84, vs 26.5 days, range 14 to 48; p=0.76).

There were no statistically significant differences in the incidence of bacterial (gram positive and gram negative), fungal, and viral infections between the two groups. It was noted that some patients had multiple infections.

The median length of hospital stay was 39 days (range 22 to 104) in the palifermin group and 42 days (range 27 to 99) in the control group (p=0.09). A summary of secondary end points is shown in Table 3.

With a median follow-up of 45.1 months (range 29.2–71.3 months) in the palifermin group and 87.3 months (range 63.4–95.5 months) in the control group, OS was not significantly different between the two groups (Fig. 3). The prevalence of 100-day non-relapse-related mortality (NRM), with relapse competing, was 9 % (95 % CI 0.05–0.15) for the entire study population. The NRM was 8 % (95 % CI 0.04–0.15) for the 99 palifermin group patients, and 10 % in the 30 control group patients (95 % CI 0.03–0.27, p=0.98). Seven patients (23.3 %) in the palifermin group and eight patients (8.1 %) in

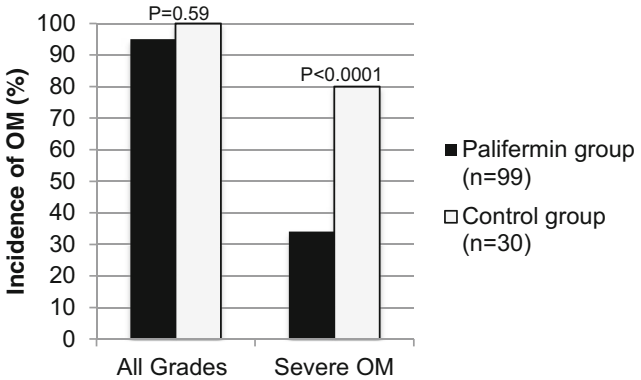

Fig. 1 Percentage of patients with OM, by group

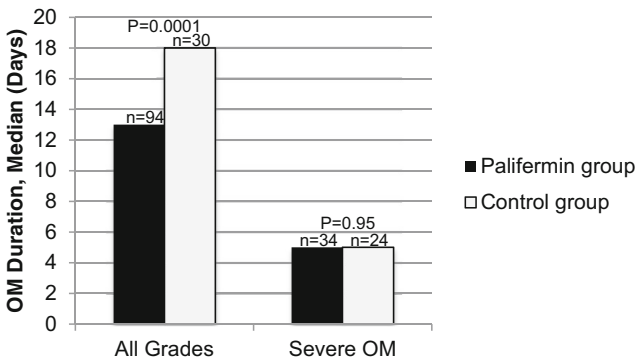

Fig. 2 Oral mucositis duration, by group

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Table 3 Summary of Secondary Endpoints

	Palifermin group (n=99)	Control group (n=30)	p value
Median duration of use (days)			
C.O.H. T.E.A.M.	13	15	0.01
PCA	14.5	22.5	0.01
TPN	25	26.5	0.76
Opioid use (mg)[a]	543	900	0.02
Incidence of infection (%)			
Bacteremia	33.3	46.7	0.2
Fungemia	3	3.3	1
Viremia	17.2	20	0.79
Duration of hospital stay (days)	39	42	0.09

C.O.H. T.E.A.M. Critical Oral Hygiene for Treatment of Edematous Aggressive Mucositis, *PCA* patient-controlled analgesia, *TPN* total parenteral nutrition

[a] IV morphine equivalents

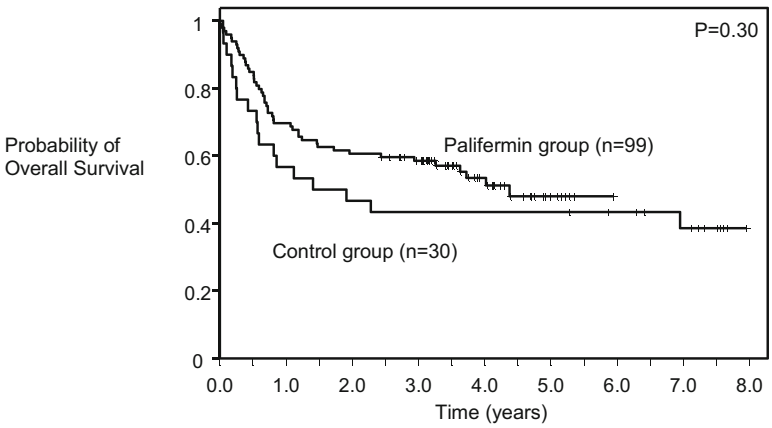
the control group died before day 100. Among patients who received palifermin, the cause of death within 100 days was related to disease progression and/or multi-organ failure in six patients and to infection in the seventh. Among the control group, the cause of death within 100 days included several factors such as GVHD, multi-organ failure, disease progression, veno-occlusive disease, and infection; post-transplant lymphoproliferative disorder was a contributing cause of death in the majority of patients.

Discussion

The goal of this research was to explore the impact of palifermin on OM in allo-HSCT among patients conditioned with FTBI and etoposide. These findings suggest that palifermin significantly reduced the incidence of severe OM and overall duration of OM after conditioning with a FTBI-based regimen as part of an allo-HSCT. Palifermin markedly reduced the incidence of severe OM, the most debilitating form of OM in which symptom management rarely provides adequate control. This result is consistent with the other clinical outcomes found to be associated with OM—median duration of C.O.H. T.E.A.M. and PCA use and quantity of opioid required for pain control were significantly less among palifermin recipients. There were no significant differences in duration of TPN use, possibly confounded by the extensive and routine use of TPN at COH.

Severe OM results in significant morbidity, impairs quality of life, and impacts health care costs. Although there were fewer patients with severe OM among those who received palifermin, this finding was not matched by a similar decrease in duration of severe OM. Confounders to these findings may have included grading and recording of OM by different

Fig. 3 Overall survival, by group



	Palifermin group (n=99)	Control group (n=30)	p-value
Overall Survival – odds ratio (95% CI)			
6 months	0.85 (0.76-0.91)	0.73 (0.54-0.86)	0.30
1 year	0.70 (0.60-0.78)	0.57 (0.37-0.72)	

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practitioners, missing OM assessments, variable frequency of OM assessment for patients who did not receive C.O.H. T.E.A.M., lack of documentation of past mucositis, oral hygiene, and plaque levels, and different GVHD prophylaxis regimens, particularly MTX-based regimens.

There are limited published studies that examine the use of palifermin in allo-HSCT patients. The severity of regimen-induced OM is dependent on the conditioning regimen and not the source of hematopoietic stem cells; thus, the ability of palifermin to reduce the incidence of severe OM in patients undergoing allo-HSCT is not expected to be different than in patients undergoing auto-HSCT, although this has not been directly evaluated in randomized studies [1]. Blazar et al. evaluated the efficacy of palifermin to prevent GVHD after allo-HSCT in a phase I/II randomized, double-blind, placebo-controlled, dose-escalation study. The conditioning regimen consisted of cyclophosphamide and TBI (Cy/TBI) in 54 patients or busulfan and cyclophosphamide (Bu/Cy) in 46 patients. Graft-versus-host disease prophylaxis included MTX given on days 1, 3, 6, and 11 post-stem cell infusion. Patients received either placebo (n=31) or palifermin (n=69) in one of four dosing schemas (8 patients receiving less and 51 patients receiving more palifermin than the current approved dose, and 10 patients receiving palifermin at the current approved dosing). There was no significant difference in acute GVHD incidence or severity, survival, or day 100 relapse rates. However, palifermin was associated with reduced incidence and mean severity of mucositis in patients conditioned with Cy/TBI (100 vs 81 % in placebo, p=0.05) but not Bu/Cy (50 % vs 44 % in placebo) [12]. The long-term follow-up study, with median follow-up of 365 days, found no difference in CMV or invasive fungal infections, chronic GVHD, or long-term survival between cohorts. The authors concluded that the benefits of palifermin are primarily limited to ameliorating mucotoxicity when given to allo-HCT recipients who receive a more mucotoxic regimen of high-dose chemotherapy with TBI but not chemotherapy alone [15].

Outside of Blazar's randomized trial, data regarding palifermin use for OM in allo-HSCT remains limited to varied findings in preclinical animal models, case reports, retrospective studies, and clinical studies with historical controls [16–20]. To date, the largest analysis of OM in allo-HSCT patients is a retrospective study in 251 patients [21]. In all patients, palifermin significantly decreased the duration of TPN use (13 vs 16 days, p=0.006), PCA use (6 vs 10 days, p=0.02), and length of hospital stay (32 vs 37 days, p=0.014). Similar to Blazar's findings, the effect of palifermin was only significant in patients who received a TBI-based conditioning regimen and not a chemotherapy-based regimen.

Analogous to our finding that there was no difference in survival with palifermin use, a long-term follow-up to 15 years in 543 patients from four randomized, placebo-controlled phase II/III studies found that the OS, progression-free survival, and the incidence of secondary malignancies were comparable between palifermin and placebo groups in patients undergoing HSCT. Further robust, long-term studies are required, but these findings suggest that there are no negative effects on long-term outcomes in patients with hematological malignancies undergoing HSCT who receive palifermin for OM prevention [22].

Although conditioning therapy is the most important cause of OM after allogeneic HSCT, the impact of MTX as GVHD prophylaxis cannot be overlooked. As an antiproliferative agent, MTX impairs mucosal regeneration after conditioning-related injury, thereby prolonging and worsening OM. A retrospective cohort analysis compared the outcomes related to OM in patients who received a GVHD prophylaxis regimen with MTX to those who did not found that patients who received a MTX-containing regimen experienced more severe OM (50 vs 7 %, p<0.05), more TPN use (43 vs 17 %, p=0.02), more days of narcotic use (17 vs 13.5 days, p=0.08), and longer length of hospital stay (22 vs 18 days, p=0.07) [23]. The current study similarly found that patients who received MTX as part of their GVHD prophylaxis regimen were more likely to develop severe OM (p<0.05).

Our findings are consistent with past studies and demonstrate a significant benefit for allo-HSCT recipients who receive a FTBI-based conditioning regimen that can potentially improve their quality of life and reduce complications and resources used during a transplant process. Although this study provides further evidence to support the use of palifermin in patients undergoing allo-HSCT after a FTBI-based conditioning regimen, a prospective randomized study is indicated to confirm these results. In particular, studies about the impact of palifermin on quality of life, adverse effects, and patient-reported outcomes, as well as a cost analysis are required to provide evidence to support the use of palifermin as standard practice in patients undergoing allo-HSCT.

In summary, palifermin was associated with reductions in the severity of OM and duration of overall OM, as well as an improvement in clinical outcomes related to OM including decreased requirements for intensive oral care treatment and opioid use, in patients receiving an allo-HSCT with FTBI-based conditioning.

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Conflict of interest This research was not sponsored by any outside organization; thus, the authors do not have a financial relationship with such organization. The authors have full control of all primary data and agree to allow the Journal to review the data if requested.

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