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Palifermin Compared to Supersaturated Calcium Phosphate Rinse in Prevention of Severe Oral Mucositis after Stem Cell Transplantation in Patients Receiving Radiotherapy-Based Myeloablative Conditioning

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Abstract: Purpose: Oral mucositis (OM) is a common, debilitating complication of conditioning regimens for hematopoietic stem cell transplantation (HSCT). Supersaturated calcium phosphate rinse (SCPR) and palifermin have shown efficacy in preventing severe OM. However, whether their efficacy differs is unknown. We aimed to compare the efficacy of SCPR and palifermin in HSCT patients receiving myeloablative conditioning. Methods: A comprehensive review of our institutional database was performed to identify patients who received myeloablative-conditioning therapy over 5 years. All HSCT patients who received radiotherapy-based myeloablative conditioning and received either palifermin or SCPR within the study period were included. Most patients received Fludarabine, Busulfan, and total body irradiation (FBT). Patients were divided into two groups based on the OM prophylactic agent received. The primary outcome is prevalence of severe OM (WHO Grade 3 and 4). The secondary outcomes are a prevalence of all-grade OM and WHO Grade 4 OM. These outcomes were compared between the two groups. Results: We identified 26 patients who received SCPR and 122 patients who received palifermin for OM prophylaxis. The prevalence of World Health Organization (WHO) Grade 3 or 4 OM was significantly lower in the palifermin group (57% vs. 100%, $p = 0.01$). In addition, the palifermin group had lower WHO Grade 4 OM (22% vs. 62%, $p = 0.0006$). The overall prevalence of OM was not significantly different between the two groups (86% for palifermin group vs. 100% for SCPR arm, $p = 0.15$). Subgroup analyses demonstrated improved outcomes with palifermin, regardless of age, sex, disease status, donor type, and primary diagnosis. Conclusion: When compared to SCPR, the use of palifermin is associated reduced severity of OM in HSCT patients receiving radiotherapy-based myeloablative conditioning.

Keywords: palifermin; supersaturated calcium phosphate rinse; mucositis; myeloablative; hematopoietic stem cell transplantation

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1. Introduction

Mucositis is one of the most debilitating adverse effects of cancer therapy. Although it can involve any part of the gastrointestinal tract, oral mucositis (OM) is particularly painful [1,2]. It often results in reduced oral intake, which further impairs nutritional status [3]. Patients that are treated for hematological malignancy are at a higher risk for mucositis, particularly those that are undergoing hematopoietic stem cell transplantation (HSCT) using myeloablative conditioning [1,3]. The incidence of OM varies based the myeloablative regimen and prophylactic agent that are used and estimated between 47 and

100% [4,5]. A systemic review of eight myeloablative studies reported an OM incidence of 73.2% [6]. In one randomized study, the incidence of Grades 3 and 4 OM was estimated to be up to 98% in patients receiving total body irradiation (TBI)-based conditioning therapy [7].

Although several agents and institutional protocols have been used to treat and prevent OM, they are either ineffective or of unconfirmed efficacy [3,8–12]. The Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) have collaborated and published guidelines for the prevention and treatment of mucositis in patients receiving antineoplastic therapy. These guidelines are updated periodically based on the emergence of evidence [13,14].

Palifermin, an intravenous recombinant human keratinocyte growth factor, is approved in United States for the prevention of OM in patients that are receiving high-dose chemotherapy with or without TBI. Palifermin has been shown in clinical trials to decrease the incidence and duration of Grades 3 and 4 OM, to minimize self-reported pain and dysphagia, and to improve physical and functional well-being [7,15,16]. Supersaturated calcium phosphate rinse (SCPR) has been shown to reduce the duration and severity of OM in patients receiving conditioning chemotherapy with or without TBI [17,18]. To date, it remains unclear whether either of these agents is superior. This study presents our institutional experience with the use of these agents in HSCT patients receiving TBI-containing myeloablative conditioning.

2. Methods

This study is a quantitative retrospective study that compares the efficacy of palifermin and SCPR in reducing the severity of OM among HSCT recipients. The data that were used in the study were extracted from the institutional database, where various variables and outcomes are tracked for all HSCT recipients.

2.1. Study Participants

This study included all subjects who underwent HSCT using TBI-containing myeloablative conditioning at a single cancer center between 1 January 2008 and 31 December 2012. Patients who received no OM prophylaxis were excluded (one patient). We reviewed the institutional database to catalogue the OM prophylactic agents that were used for each subject. Electronic and paper medical records were also reviewed when necessary. Subjects were divided into two groups based on the type of OM prophylactic agent that was used; one group received SCPR and the other received palifermin.

2.2. Conditioning Regimens

Subjects in the study received chemotherapeutic conditioning regimens using standard myeloablative dosing [19]. The most common conditioning regimen that was used was intravenous fludarabine at a dose of 50 mg/m^2 daily for 5 consecutive days (days −6 to −2, inclusive), intravenous busulfan at a dose of 3.2 mg/kg of adjusted body weight daily for 4 days (days −5 to −2, inclusive), and TBI at a dose of 200 cGy daily for 2 consecutive days (days −1 and 0). This regimen is collectively known as the FBT regimen. When used, cyclophosphamide was administered at a dose of 60 mg/kg daily for 2 days and etoposide was used as a single dose at 2560 mg/m^2 at day −3. Those who received cyclophosphamide and/or etoposide were administered TBI at a dose of 1200 cGy divided over 4 days. All patients who received non-TBI containing regimens were excluded from the study (134 patients). Notably, the use of these regimens has decreased remarkably over the last decade due to their high toxicity and the emergence of other less toxic regimens.

2.3. Study Drugs

SCPR was self-administered at a dose of 71 mg/30 mL four times per day as oral rinse, starting on the day of HSCT and until full engraftment or resolution of OM, whichever was later [20]. Palifermin was administered as 2 episodes of 3 consecutive daily doses of 60 μg/kg intravenously given 3 days before initiation of conditioning and again starting

1 to 2 days after HSCT [7]. The doses and timing of administration were universally set by the transplant center. The choice of OM prophylactic agent was based on Program Standard Operative Procedure extant at the time of HSCT and not related to the recipient or donor characteristics. In the period from 1 January 2008 to 31 March 2010, all patients received palifermin. During the period from 1 April 2010, and 31 October 2010, all patients received SCPR except those who received high-dose cyclophosphamide, which received palifermin (2 patients). During the period of 1 November 2010 to 31 December 2012, all patients received palifermin. Cryotherapy was not used as it was not included as part of the transplant protocol for patients receiving non-melphalan-based conditioning regimen according to the Program Standard Operative Procedure. The Program Standard Operative Procedure was established and modified by the transplant committee, which met periodically to discuss and make the necessary changes based on the available literature in the field. None of the patients in either group received methotrexate for prophylaxis against graft-versus-host disease.

2.4. Study Outcomes

The primary aim of this study was to compare palifermin to SCPR in reducing the severity of OM (decreasing Grade 3 and 4 OM). The secondary outcomes are to compare palifermin to SCPR in reducing all-grade OM and to compare palifermin to SCPR in reducing Grade 4 OM. We also assessed whether age, sex, primary diagnosis, donor type, or disease status predicted development of severe OM (Grade 3 and 4). Finally, we assessed whether either agent was superior to the other in specific subsets of patients as stratified by age, sex, primary diagnosis, donor type, disease status, and disease type.

As part of the institutional procedure, patients are assessed daily for the development and severity of OM by an experienced transplant physician at the beginning of the day of transplantation and continuing until neutrophil engraftment or resolution of OM, whichever was later. OM was graded according to the five-grade World Health Organization (WHO) toxicity scale [21]. The documented OM grade of each patient is the maximum OM grade that is encountered by that patient throughout his/her course of HSCT, which we will refer to as OM grade in the reminder of this manuscript. This information is stored in an institutional database to assist in tracking of the outcomes of the transplant center and to provide basis for quality improvement. This information was extracted after obtaining institutional review board approval and were then analyzed in this study.

During the study period, patients who developed OM were treated according to institutional guidelines. Choice of therapy included chlorhexidine, antimicrobial agents, analgesics, local anesthetics, and others. Palifermin was not used for the treatment of OM. SCPR was continued if OM developed and continued until the resolution of oral lesions. Oral acyclovir or a similar anti-herpetic agent was administered to all patients as prophylaxis for herpes zoster virus reactivation starting 3 days before initiation of conditioning therapy and continued for at least 2 years after HSCT [22].

2.5. Statistical Analysis

The baseline characteristics of subjects were categorized (when appropriate) and compared between two groups using the Student's *t*-test for continuous variable (age) and chi-square or Fisher's exact test (if indicated) for categorical variables. The overall prevalence of OM, prevalence of severe OM (Grade 3 and 4), and prevalence of Grade 4 OM were analyzed using logistic regression. Estimates were calculated using an odds ratio (OR). The firth method was used due to the complete quasi-separation of the data points for the severe OM and all-grade OM. A Cochran–Armitage trend test was used to compare the trend of OM grades between the groups. Multivariable analyses were conducted to identify predictors of severe OM. Subgroup analyses were performed by stratifying the data into groups using various variables (age, gender, disease status, donor type, conditioning regimen, and disease type). Forest plots were used to display the results for the primary

outcome. Analysis of all subgroups was performed using Firth method. All tests used were two-sided and a significance level of 0.05 was used.

3. Results

A total of 148 patients underwent HSCT using TBI-containing conditioning regimens at the Western Pennsylvania Cancer Institute in Pittsburgh, Pennsylvania, over the five-year study period. Of these, 26 received SCPR and 122 received palifermin. The baseline characteristics of the patients were comparable between the two groups (Table 1). Notably, the palifermin group had higher proportion of patients with myeloid disorders and the SCPR group had higher proportion of patients with lymphoid disorders. However, this difference was not statistically significant ($p = 0.1$).

Table 1. Comparison of the patients' characteristics between the two groups.

Variable.	SCPR [a] Group N = 26 (%)	Palifermin Group N = 122 (%)
Age-years		
Mean ± SD [b]	51 ± 13.9	50 ± 12.6
Range	(23–68)	(20–74)
Female-n (%)	11 (42)	55 (45)
Diagnosis—n (%)		
Lymphoid disorder	18 (69)	63 (52)
Non-lymphoid disorder	8 (31)	59 (48)
Myeloid disorder	7	55
Plasma cell disorder	0	2
Others	1	2
Conditioning Regimen—n (%)		
FBT [c]	26 (100)	116 (95)
Others	0 (0)	6 (5)
FCT [d]	0	3
CT [e]	0	2
VT [f]	0	1
Donor—n (%)		
Autologous	8 (31)	42 (34)
Allogeneic	18 (69)	72 (59)
Umbilical cord	0 (0)	8 (7)
Disease Status—n (%)		
In complete remission	12 (46)	51 (42)
Not in complete remission	14 (54)	71 (58)

[a] Supersaturated calcium phosphate rinse, [b] SD: Standard deviation, [c] Fludarabine, busulfan, and TBI, [d] Fludarabine, cyclophosphamide, and TBI, [e] Cyclophosphamide and TBI, [f] Etoposide (VP-16) and TBI.

3.1. Efficacy

Within the SCPR group, all 26 patients (100%) developed Grade 3 or 4 OM compared to 69 (57%) in the palifermin group (Table 2). The prevalence of Grade 3 and 4 OM was significantly lower in those who received palifermin compared to SCPR (OR = 0.03, $p = 0.01$). This indicates a 97% reduction of the prevalence of Grade 3 or 4 OM in the palifermin group compared to the SCRP group. Grade 4 OM developed in 16 patients (62%) who received SCPR compared to 27 patients (22%) who received palifermin. The prevalence of Grade 4 OM was 81% lower in those who received palifermin compared to SCPR (OR = 0.19, $p = 0.0006$). In the SCPR group, all 26 patients (100%) developed OM compared to 105 of 122 patients (86%) in the palifermin group. The overall prevalence of OM was not significantly different between the two groups (OR = 0.14, $p = 0.15$). There was a statistically significant trend toward lower grades of OM in the palifermin group compared to the SCPR group ($p < 0.0001$ using trend test, Figure 1).

Table 2. Prevalence and severity of oral mucositis.

Variable	Palifermin Group N = 122	SCPR [a] Group N = 26	Adjusted OR [b]	*p*–Value	95% CI [c] for OR
Overall OM prevalence—n (%)	105 (86)	26 (100)	0.136	0.15	0.009 to 2.08 [d]
Prevalence of WHO [e] grade $\frac{3}{4}$ [f]—n (%)	69 (57)	26 (100)	0.026	0.01	0.002 to 0.41 [d]
Prevalence of WHO grade 4 [f]—n (%)	27 (22)	16 (62)	0.191	0.0006	0.07 to 0.49

[a] SCPR: Supersaturated calcium phosphate rinse, [b] OR: Odds ratio, [c] CI: Confidence interval, [d] Estimates of this variable were calculated using the Firth method, [e] World Health Organization, [f] Grade refers to the maximum oral mucositis grade encountered by the patient.

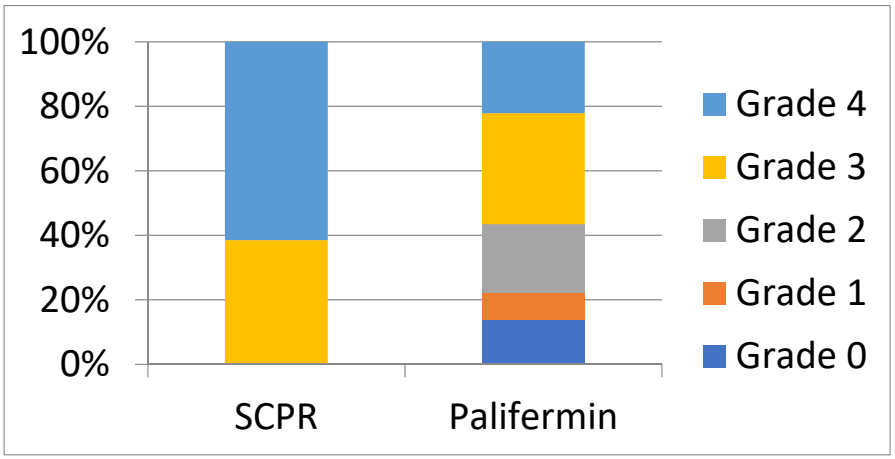

Figure 1. Bar chart showing the distribution of maximum OM grades among patients in the two groups (%).

3.2. Prediction of Severe Grades of OM

Multivariable analyses were conducted to predict the impact of various variables on the severity of OM. Variables included in the analyses were the type of OM prophylactic agent that was used, age, sex, primary diagnosis, donor type, and disease status at the time of HSCT. Among these variables, type of prophylactic agent was the only variable predictive of development of Grade 3 or 4 OM (OR = 0.03, $p = 0.01$, Table 3).

Table 3. Prediction of severe OM using various variables.

Variable	OR [a]	*p*-Value	95% CI [b] for OR
Agent used (palifermin vs. SCPR [c])	0.03	0.01	0.002–0.413
Age (year)	0.97	0.1	0.943–1.005
Gender (female vs. male)	0.85	0.67	0.39–1.83
Diagnosis (lymphoid vs. non-lymphoid disorders)	1.19	0.69	0.5–2.85
Conditioning Regimen (FBT [d] vs. other)	7.25	0.69	0.79–66.7
Donor			
allogeneic vs. autologous	0.87	0.78	0.33–2.27
UC [e] vs. autologous	4.19	0.2	0.47–37.16
Disease Status (in CR [f] vs. not in CR)	1.28	0.54	0.58–2.83

[a] OR: Odds ratio, [b] CI: Confidence interval, [c] SCPR: Supersaturated calcium phosphate rinse, [d] FBT: Fludarabine, busulfan, and TBI, [e] UC: Umbilical cord, [f] CR: Complete remission. All estimates of this variable were calculated using the Firth method.

3.3. Subgroup Analysis

Preplanned subgroup analyses were conducted to evaluate whether the superiority of palifermin over SCPR was restricted to specific subgroups. Subgroups were created using various variables. There was a notable consistent trend toward a lower prevalence of severe OM with the use of palifermin compared to SCPR among all the subgroups (Figure 2).

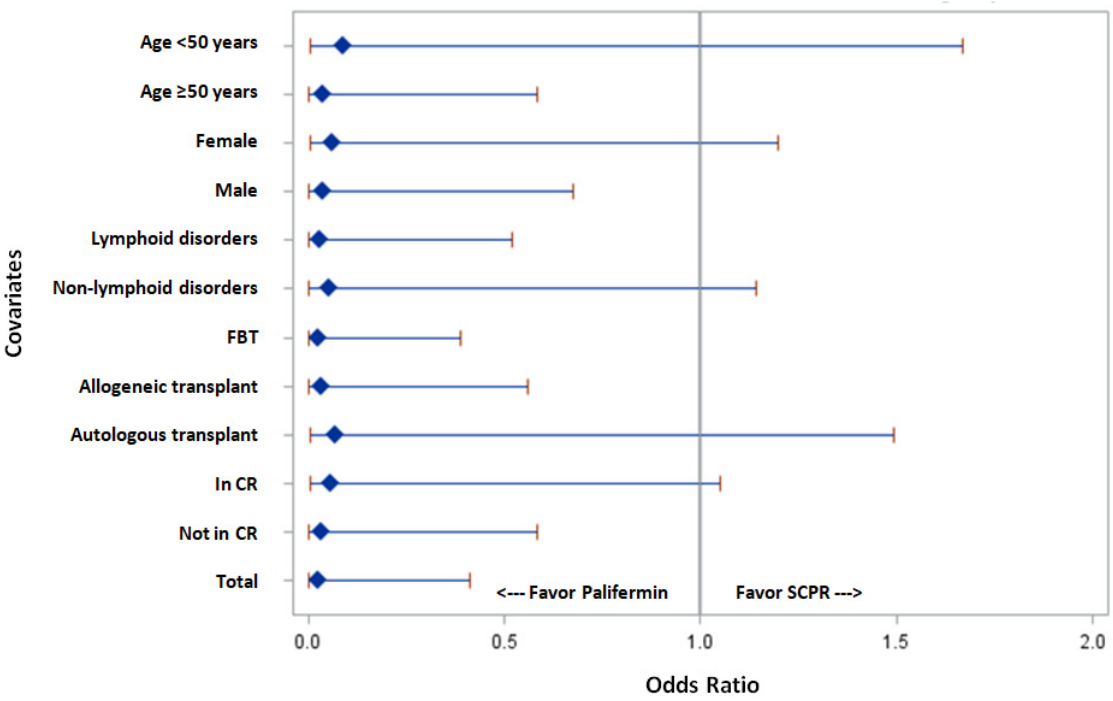

Figure 2. Forest plot showing the prevalence of severe OM among various subgroups.

4. Discussion

Palifermin is a recombinant keratinocyte growth factor with biologically similar activity to fibroblast growth factor-7 [23]. The mechanism of action of palifermin appears to involve stimulation of epithelial proliferation, modulation of clonogenic cell death, and alteration of various cytokines [24,25]. Previous studies have demonstrated the superiority of palifermin to placebo in reducing the severity and duration of OM, oral pain, and the need for parenteral nutrition in HSCT patients receiving chemotherapy with or without TBI [7,8,15,26]. SCPR is an oral rinse with a high concentration of calcium and phosphorus ions. The exact mechanism of action of SCPR is not known. However, it readily diffuses into mucosal tissue and mucositis lesions. Calcium and phosphorus ions are thought to play a major role in intracellular signaling, inflammation, and mucosal repair [18]. SCPR has been shown to lower mean measures of oral toxicity, oral pain, and OM duration compared to controls in HSCT patients receiving TBI- and/or chemotherapy-based conditioning [17,18]. In this study, the administration of palifermin resulted in a notable reduction in the prevalence of severe OM compared to SCPR. In addition, the benefit of palifermin appears to be consistent across various subgroups, suggesting that demographic variables, disease variables, and donor type have little influence on the outcome of therapy.

The heterogeneity of the conditioning regimens that were used in prior studies makes generalization of the results difficult, particularly as it relates to comparison of the efficacy of palifermin and SCPR. In contrast, most patients in this study received FBT conditioning. A minority received TBI in combination with other conditioning chemotherapeutic agents at doses that are known to cause severe mucositis. Therefore, the results of this study can reasonably be applied to patients receiving FBT therapy. Notably, the prevalence of Grade 3 and 4 mucositis among patients who received SCPR in this study (100%) is comparable to the previously reported incidences when a placebo was used (98%) [7],

which suggests that SCPR is ineffective in preventing OM in this patient population. Interestingly, recently published studies showed that palifermin may have limited efficacy in chemotherapy-induced OM, particularly in high-dose melphalan-induced OM [26,27]. Our study suggests the efficacy of palifermin in preventing severe OM in patients receiving chemoradiotherapy myeloablative conditioning. MASCC-ISOO has initially published comprehensive guidelines for the prevention and treatment of mucositis in 2004 [28]. In 2014, the updated guidelines recommended the use of palifermin in patients receiving high-dose chemotherapy and TBI, followed by autologous HSCT, for a hematological malignancy but provided no guidelines for the use of SCPR [14]. In the most recent guidelines that were published in 2020, no guidelines were possible for either palifermin or SCPR due to conflicting evidence [13].

The pathobiology of OM is remarkably complex. It was once thought to be secondary to direct mucosal injury inflicted by cytotoxic therapy [29–32]. The beneficial effect of cryotherapy in preventing high-dose melphalan-induced OM supports this hypothesis. Cryotherapy results in vasoconstriction, which limits the exposure of the oral mucosa to melphalan and, therefore, decreases the severity of OM [33,34]. Recently, a more complex five-phase model was developed to elucidate the pathogenesis of OM [35]. However, this model continues to view OM as a universal outcome regardless of the causative agent. The differential benefit of palifermin in TBI-induced OM but not in melphalan-induced OM suggests a fundamental difference in the pathobiology. Interestingly, the nrf2 pathway has been extensively implicated in radiotherapy-induced mucosal injury [25,36]. Palifermin is thought to exert its OM prophylactic effect through this pathway, which may explain the superiority of palifermin over SCPR in TBI-induced mucosal injury [24,25].

Despite advances in the treatment and prevention of OM, prediction of who is at risk remains a difficult task. There is a significant gap in the literature on which host, donor, and disease variables alter this risk. In our exploratory multivariable analysis, none of the tested variables were predictive of development of severe OM, except the type of prophylactic agent employed. A recent study has identified a common deletion polymorphism in the GSTM1 and GSTT1 genes, which results in a lack of glutathione-S-transferase activity and a two-fold increased risk of OM [25,36]. If replicated, this may present an attractive method to predict the incidence of OM and its severe forms, which may allow clinicians to deploy more aggressive OM preventive measures to those that are at risk.

The efficacy of palifermin in preventing severe OM is faced with its high cost. According to the Center of Medicare and Medicaid, the cost of 50 mcg of palifermin is $21.275. Therefore, the cost of palifermin for a 70 kg patient is estimated to be $10,722.60 [37]. A 30 day supply of SCPR has a retail cost of $826.30 [38]. Compared to no prophylaxis, palifermin was associated with favorable economic outcome in a large cost-effectiveness study. After accounting for all costs incurred, palifermin was associated with a non-significant mean cost-saving of $3595. Moreover, these findings were robust to all plausible values of costs with cost-saving that can reach $5103 per patient [39]. Nonetheless, whether palifermin will continue to be cost saving and/or cost-effective if compared to SCPR remains uncertain.

Novel modalities to prevent OM continue to emerge. Photo-biomodulation has been shown to prevent radiotherapy-induced OM. The efficacy appears to be robust, particularly in the setting of HSCT [40,41]. However, their efficacy as compared to pharmacologic therapy or in combination is yet to be elucidated. The updated MASCC/ISOO guidelines recommend the use of photo-biomodulation for the prevention of OM in HSCT and head and neck cancer patients receiving mucotoxic therapy [13]. Combining photo-biomodulation with pharmacologic therapy to prevent OM could potentially be effective and should be considered for future research.

5. Limitations

There are several limitations of this study. Most of our patients received lower dose TBI (400 cGy) than what was used in most other studies. Nonetheless, the prevalence of

Grade 3 or 4 OM that was incurred in our patients was 57%, which is comparable to the incidence of 63% reported with a TBI dosing of 1200 cGy [35]. Moreover, the retrospective design of our study and hospital policy-driven selection of OM prophylactic therapy may be susceptible to bias. Prophylactic therapy was administered according to institutional protocols during the time under study and was not based on any specific patient, disease, or donor characteristics. Additionally, our study was 10-years old and some of conditioning regimens, HSCT protocols, and MASCC/ISOO guidelines have changed and, therefore, these results may not be applicable to some subjects, particularly those that are receiving chemotherapy-only conditioning (without radiotherapy) or receiving additional effective supportive measures. Moreover, a comprehensive oral examination to treat and eliminate all the potential sources of oral infection is now recommended for all patients undergoing HSCT. This was not part of the institutional procedure at the time when this study was conducted, which could potentially introduce some bias. Finally, our study evaluated the prevalence and severity of OM but not oral pain, analgesic use, use of parenteral nutrition, systemic infection, length of hospital stays, or physical and psychological well-being. Yet these parameters are predominantly influenced by the development of OM, particularly severe grades, which makes our outcome measures reasonable surrogates of these parameters.

In conclusion, this study suggests that palifermin is potentially more effective than SCPR in reducing the severity of OM in HSCT patients receiving TBI-containing myeloablative conditioning therapy. Based on this study and others, palifermin could be considered for OM prophylaxis in HSCT patients receiving myeloablative TBI-containing conditioning. However, further studies are needed to determine the optimal OM prophylactic strategy in TBI-containing and non-TBI-containing conditioning regimens and explore the potential synergistic effect of combination therapy in preventing OM.

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Informed Consent Statement: The need for informed consent form was waived by the institutional review board.

Data Availability Statement: The data is not publicly available due to privacy and ethical restrictions.

Conflicts of Interest: All authors disclose no conflict of interest or competing interest related to this manuscript and this study.

Abbreviations

OM	Oral mucositis
HSCT	Hematopoietic stem cell transplantation
TBI	Total body irradiation
SCPR	Supersaturated calcium phosphate rinse
FBT	Fludarabine, busulfan, and total body irradiation
WHO	World Health Organization
OR	Odds ratio
FCT	Fludarabine, cyclophosphamide, and total body irradiation
CT	Cyclophosphamide and total body irradiation
VT	Etoposide and total body irradiation

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