Palifermin Compared to Supersaturated Calcium Phosphate Rinse in Prevention of Severe Oral Mucositis after Stem Cell Transplantation

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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. Most patients received Fludarabine, Busulfan and total body irradiation (FBT).

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: As compared to SCPR, the use of palifermin is associated reduced severity of OM in HSCT patients receiving radiotherapy-based myeloablative conditioning.

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 [18, 35]. It often results in reduced oral intake, which further impairs nutritional status [22]. Patients treated for hematological malignancy are at higher risk for mucositis, particularly those undergoing hematopoietic stem cell transplantation (HSCT) using myeloablative conditioning [18, 22]. The incidence of OM varies based the myeloablative regimen used and prophylactic agent used and estimated between 47 and 100% [2, 36]. A systemic review of 8 myeloablative studies reported an OM incidence of 73.2% [9]. 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 [30].

Although several agents and institutional protocols have been used to treat and prevent OM, they are either ineffective or of unconfirmed efficacy [7, 11, 12, 22, 24, 33]. Palifermin, an intravenous recombinant human keratinocyte growth factor, is approved in United States for prevention of OM in patients 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 [17, 25, 30]. 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 [19, 23]. 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.

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 used in the study were extracted from the institutional database, where various variables and outcomes are tracked for all HSCT recipients.

Study Participants

This study included all subjects who underwent HSCT using a TBI-containing myeloablative conditioning at single cancer between January 1, 2008, and December 31, 2012. Patients who received no OM prophylaxis were excluded (one patient). We reviewed the institutional database to catalogue the OM prophylactic agent 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 used; one group received SCPR and the other received palifermin.

Conditioning Regimens

Subjects in the study received chemotherapeutic conditioning regimens using standard myeloablative dosing [3]. The most common conditioning regimen used was intravenous fludarabine at a dose of 50 mg/m2 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 is used as a single dose at 2560 mg/m2 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).

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 [21]. 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 [31]. 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 January 1, 2008, and March 31, 2010, all patients received palifermin. During the period from April 1, 2010, and October 31, 2010, all patients received SCPR except those who received high-dose cyclophosphamide, which received palifermin (2 patients). During

the period of November 1, 2010, and December 31, 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.

Study Outcomes

The primary aim of this study is 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 predict development of severe OM (grade 3 and 4). Finally, we assessed whether either agent is 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 beginning on the day of transplantation and continuing until neutrophil engraftment or resolution of OM, whichever is later. OM was graded according to the five-grade world health organization (WHO) toxicity scale [20]. This information is stored in an institutional database to assist in tracking the outcomes of the transplant center and to provide basis for quality improvement. This information was extracted after obtaining institutional review board approval and 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 treatment of OM. SCPR was continued if OM developed and continued until resolution of oral lesions. Oral acyclovir or 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 [37].

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 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. 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. A significance level of 0.05 was used.

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 are comparable between the two groups (Table 1). Notably, the palifermin group has higher proportion of patients with myeloid disorders and the SCPR group has higher proportion of patients with lymphoid disorders. However, this difference was not statistically significant (p= 0.1).

Table 1: Patients' characteristics compared between the two groups

Variable	SCPRa group N=26 (%)	Palifermin group N=122 (%)
Age-years		
Mean ± SDb	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 (%)		
FBTc	26 (100)	116 (95)
Others	0 (0)	6 (5)
FCTd	0	3
CTe	0	2
VTf	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)

aSupersaturated calcium phosphate rinse, bSD: Standard deviation, cFludarabine, busulfan and TBI, dFludarabine, cyclophosphamide, and TBI, eCyclophosphamide and TBI, fEtoposide (VP-16) and TBI.

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 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 is a statistically significant trend toward lower grades of OM in the palifermin group compared to SCPR group (p<0.0001 using trend test, Figure 1).

Table 2: Prevalence and severity of oral mucositis

Variable	Palifermin group N=122	SCPRa group N=26	Adjusted ORb	p value	95% Clc for OR
Overall OM prevalence – n (%)	105 (86)	26 (100)	0.136	0.15	0.009 to 2.08d
Prevalence of WHOe grade 1/2 – n (%)					
Prevalence of WHO grade 3/4 – n (%)	69 (57)	26 (100)	0.026	0.01	0.002 to 0.41d
Prevalence of WHO grade 4 – n (%)	27 (22)	16 (62)	0.191	0.0006	0.07 to 0.49

aSCPR: Supersaturated calcium phosphate rinse, bOR: Odds ratio, cCI: Confidence interval, dEstimates of this variable were calculated using the firth method, eWorld Health Organization

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 are type of OM prophylactic agent 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	ORa	P-value	95% CIb for OR
Agent used (palifermin vs SCPRc)	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 - (FBTd vs other)	7.25	0.69	0.79-66.7
Donor			
allogeneic vs autologous	0.87	0.78	0.33-2.27
UCe vs autologous	4.19	0.2	0.47-37.16
Disease Status - (in CRf vs not in CR)	1.28	0.54	0.58-2.83

aOR: Odds ratio, 2CI: Confidence interval, cSCPR: Supersaturated calcium phosphate rinse, dFBT: Fludarabine, busulfan and TBI, eUC: Umbilical cord, fCR: Complete remission. All estimates of this variable were calculated using the firth method.

Subgroup analysis

A 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 is a notable consistent trend toward lower prevalence of severe OM with the use of palifermin compared to SCPR among all subgroups (Figure 2).

Discussion

Palifermin is a recombinant keratinocyte growth factor with biologically similar activity to fibroblast growth factor-7 [4]. The mechanism of action of Palifermin appears to involve stimulation of epithelial proliferation, modulation of clonogenic cell death, and alteration of various cytokines [6, 27]. 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, 14, 17, 30]. 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 [19]. 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 [19, 23]. In this study, 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 used in prior studies makes generalization of 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 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 incidence when placebo is used (98%) [30] , 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 [5, 14]. Our study suggests the efficacy of palifermin in preventing severe OM in patients receiving chemoradiotherapy myeloablative conditioning.

The pathobiology of OM is remarkably complex. It was once thought to be secondary to direct mucosal injury inflicted by cytotoxic therapy [10, 28, 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 [1, 34]. Recently, a more complex five-phase model was developed to elucidate the pathogenesis of OM [26]. 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 [16, 27]. 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 [6, 27].

Despite advances in 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 proved 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 [16, 27]. 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 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 50mcg of palifermin is $21.275. Therefore, the cost of palifermin for a 70kg patient is estimated to be $10,722.6 [8]. A 30 day supply of SCPR has a retail cost of $826.30 [15]. 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 $3,595. Moreover, these findings were robust to all plausible values of costs with cost-saving that can reach $5,103 per patient [13]. Nonetheless, whether palifermin will continue to be cost saving and/or cost-effective if compared to SCPR remains uncertain.

Limitations

There are several limitations of this study. Most of our patients received lower dose TBI (400 cGy) than used in most other studies. Nonetheless, the prevalence of grade 3 or 4 OM incurred in our patients was 57%, which is comparable to the incidence of 63% reported with TBI dosing of 1200 cGy [26]. 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 extant during the time under study and was not based on any specific patient, disease, or donor characteristics. Additionally, these results may not be applicable to subjects receiving chemotherapy-only conditioning (without radiotherapy). 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.

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

Declarations

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

Consent for publications: All authors have reviewed the manuscript, agree with its contents, and consent to its submission.

References

1. Aisa Y, Mori T, Kudo M, Yashima T, Kondo S, Yokoyama A, Ikeda Y, Okamoto S (2005) Oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 13: 266-269
2. Andersson BS, Thall PF, Madden T, Couriel D, Wang X, Tran HT, Anderlini P, de Lima M, Gajewski J, Champlin RE (2002) Busulfan systemic exposure relative to regimen-related toxicity and acute graft-versus-host disease: Defining a therapeutic window for i.v. BuCy2 in chronic myelogenous leukemia Biol Blood Marrow Transplant 8: 477-485
3. Atilla E, Ataca Atilla P, Demirer T (2017) A Review of Myeloablative vs Reduced Intensity/Non-Myeloablative Regimens in Allogeneic Hematopoietic Stem Cell Transplantations Balkan medical journal 34: 1-9
4. Beaven AW, Shea TC (2006) Palifermin: a keratinocyte growth factor that reduces oral mucositis after stem cell transplant for haematological malignancies Expert opinion on pharmacotherapy 7: 2287-2299

5. Blijlevens N, de Chateau M, Krivan G, Rabitsch W, Szomor A, Pytlik R, Lissmats A, Johnsen HE, de Witte T, Einsele H, Ruutu T, Niederwieser D (2012) In a high-dose melphalan setting, palifermin compared with placebo had no effect on oral mucositis or related patient's burden Bone marrow transplantation
6. Blijlevens N, Sonis S (2007) Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 18: 817-826
7. Campbell P, Friebe A, Foulstone P, Grigg A, Hempton J, Bajel A (2012) Impact of palifermin on mucosal toxicity in autologous stem cell transplants using busulfan-melphalan conditioning chemotherapy for Hodgkin and non-Hodgkin lymphoma Leukemia & lymphoma 53: 1415-1416
8. Centers for Medicare and Medicaid Services (2019) October 2019 ASP Pricing File (Updated 09/30/19). https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.htmlAccessed. Accessed 15 October 2019
9. Chaudhry HM, Bruce AJ, Wolf RC, Litzow MR, Hogan WJ, Patnaik MS, Kremers WK, Phillips GL, Hashmi SK (2016) The Incidence and Severity of Oral Mucositis among Allogeneic Hematopoietic Stem Cell Transplantation Patients: A Systematic Review Biol Blood Marrow Transplant 22: 605-616
10. Dodd M (2004) The pathogenesis and characterization of oral mucositis associated with cancer therapy Oncology nursing forum 31: 5-11
11. Dodd MJ, Miaskowski C, Greenspan D, MacPhail L, Shih AS, Shiba G, Facione N, Paul SM (2003) Radiation-induced mucositis: a randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes Cancer investigation 21: 21-33
12. El-Sayed S, Nabid A, Shelley W, Hay J, Balogh J, Gelinas M, MacKenzie R, Read N, Berthelet E, Lau H, Epstein J, Delvecchio P, Ganguly PK, Wong F, Burns P, Tu D, Pater J (2002) Prophylaxis of radiation-associated mucositis in conventionally treated patients with head and neck cancer: a double-blind, phase III, randomized, controlled trial evaluating the clinical efficacy of an antimicrobial lozenge using a validated mucositis scoring system Journal of clinical oncology : official journal of the American Society of Clinical Oncology 20: 3956-3963
13. Elting LS, Shih YC, Stiff PJ, Bensinger W, Cantor SB, Cooksley C, Spielberger R, Emmanoulides C (2007) Economic impact of palifermin on the costs of hospitalization for autologous hematopoietic stem-cell transplant: analysis of phase 3 trial results Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 13: 806-813
14. Goldberg JD, Zheng J, Castro-Malaspina H, Jakubowski AA, Heller G, van den Brink MR, Perales MA (2013) Palifermin is efficacious in recipients of TBI-based but not chemotherapy-based allogeneic hematopoietic stem cell transplants Bone marrow transplantation 48: 99-104
15. GoodPx (2019) Neutrasal. https://www.goodrx.com/neutrasal?form=carton&dosage=120-packets&quantity=1&days_supply=&label_override=Neutrasal. Accessed 15 October 2019

16. Hahn T, Zhelnova E, Sucheston L, Demidova I, Savchenko V, Battiwalla M, Smiley SL, Ambrosone CB, McCarthy PL, Jr. (2010) A deletion polymorphism in glutathione-S-transferase mu (GSTM1) and/or theta (GSTT1) is associated with an increased risk of toxicity after autologous blood and marrow transplantation Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 16: 801-808
17. Horsley P, Bauer JD, Mazkowiack R, Gardner R, Bashford J (2007) Palifermin improves severe mucositis, swallowing problems, nutrition impact symptoms, and length of stay in patients undergoing hematopoietic stem cell transplantation Support Care Cancer 15: 105-109
18. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA, McGuire DB, Hutchins RD, Peterson DE (2007) Updated clinical practice guidelines for the prevention and treatment of mucositis Cancer 109: 820-831
19. Markiewicz M, Dzierzak-Mietla M, Frankiewicz A, Zielinska P, Koclega A, Kruszelnicka M, Kyrcz-Krzemien S (2012) Treating oral mucositis with a supersaturated calcium phosphate rinse: comparison with control in patients undergoing allogeneic hematopoietic stem cell transplantation Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20: 2223-2229
20. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment Cancer 47: 207-214
21. MPR (2019) Caphosol Rx. https://www.empr.com/drug/caphosol/. Accessed 15 October 2019
22. Niscola P (2010) Mucositis in malignant hematology Expert Rev Hematol 3: 57-65
23. Papas AS, Clark RE, Martuscelli G, O'Loughlin KT, Johansen E, Miller KB (2003) A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation Bone marrow transplantation 31: 705-712
24. Pytlik R, Benes P, Patorkova M, Chocenska E, Gregora E, Prochazka B, Kozak T (2002) Standardized parenteral alanyl-glutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo controlled study Bone marrow transplantation 30: 953-961
25. Raber-Durlacher JE, von Bultzingslowen I, Logan RM, Bowen J, Al-Azri AR, Everaus H, Gerber E, Gomez JG, Pettersson BG, Soga Y, Spijkervet FK, Tissing WJ, Epstein JB, Elad S, Lalla RV (2013) Systematic review of cytokines and growth factors for the management of oral mucositis in cancer patients Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 21: 343-355
26. Sonis ST (2009) Mucositis: The impact, biology and therapeutic opportunities of oral mucositis Oral oncology 45: 1015-1020
27. Sonis ST (2011) Oral mucositis Anti-cancer drugs 22: 607-612
28. Sonis ST, Lindquist L, Van Vugt A, Stewart AA, Stam K, Qu GY, Iwata KK, Haley JD (1994) Prevention of chemotherapy-induced ulcerative mucositis by transforming growth factor beta 3 Cancer research 54: 1135-1138

29. Sonis ST, Peterson RL, Edwards LJ, Lucey CA, Wang L, Mason L, Login G, Ymamkawa M, Moses G, Bouchard P, Hayes LL, Bedrosian C, Dorner AJ (2000) Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters Oral oncology 36: 373-381
30. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, Shea T, Yanovich S, Hansen K, Noga S, McCarty J, LeMaistre CF, Sung EC, Blazar BR, Elhardt D, Chen M-G, Emmanouilides C (2004) Palifermin for Oral Mucositis after Intensive Therapy for Hematologic Cancers New England Journal of Medicine 351: 2590-2598
31. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, Shea T, Yanovich S, Hansen K, Noga S, McCarty J, LeMaistre CF, Sung EC, Blazar BR, Elhardt D, Chen M-G, Emmanouilides C (2004) Palifermin for Oral Mucositis after Intensive Therapy for Hematologic Cancers N Engl J Med 351: 2590-2598
32. Stiff P (2001) Mucositis associated with stem cell transplantation: current status and innovative approaches to management Bone marrow transplantation 27 Suppl 2: S3-S11
33. Stokman MA, Spijkervet FK, Burlage FR, Dijkstra PU, Manson WL, de Vries EG, Roodenburg JL (2003) Oral mucositis and selective elimination of oral flora in head and neck cancer patients receiving radiotherapy: a double-blind randomised clinical trial British journal of cancer 88: 1012-1016
34. Tartarone A, Matera R, Romano G, Vigliotti ML, Di Renzo N (2005) Prevention of high-dose melphalan-induced mucositis by cryotherapy Leukemia & lymphoma 46: 633-634
35. Tooley KL, Howarth GS, Butler RN (2009) Mucositis and non-invasive markers of small intestinal function Cancer biology & therapy 8: 753-758
36. Vokurka S, Steinerova K, Karas M, Koza V (2009) Characteristics and risk factors of oral mucositis after allogeneic stem cell transplantation with FLU/MEL conditioning regimen in context with BU/CY2 Bone Marrow Transplant 44: 601-605
37. Yahav D, Gafter-Gvili A, Muchtar E, Skalsky K, Kariv G, Yeshurun M, Leibovici L, Paul M (2009) Antiviral prophylaxis in haematological patients: systematic review and meta-analysis Eur J Cancer 45: 3131-3148

Figures

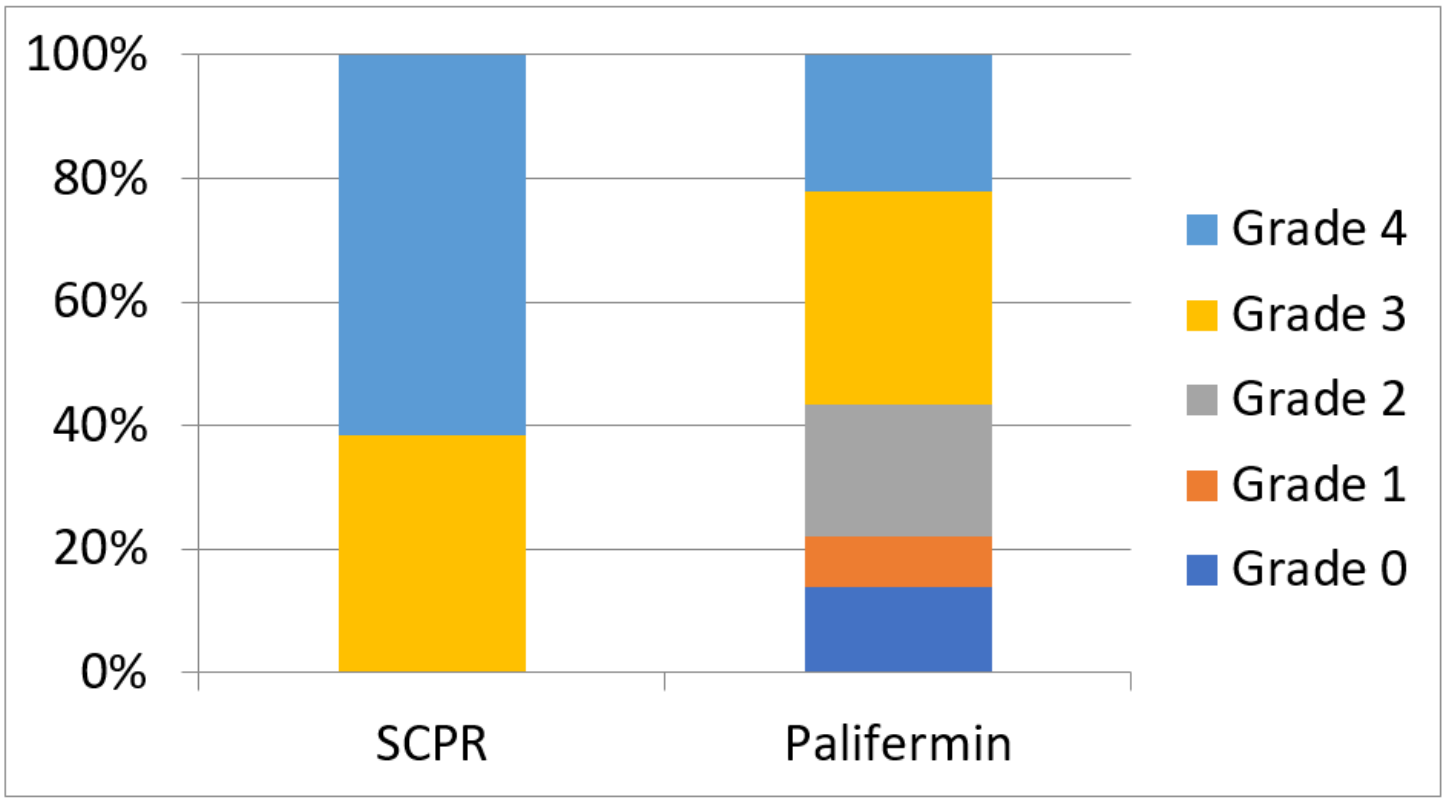

Figure 1

Bar chart showing the distribution of OM grades among the two groups (%)

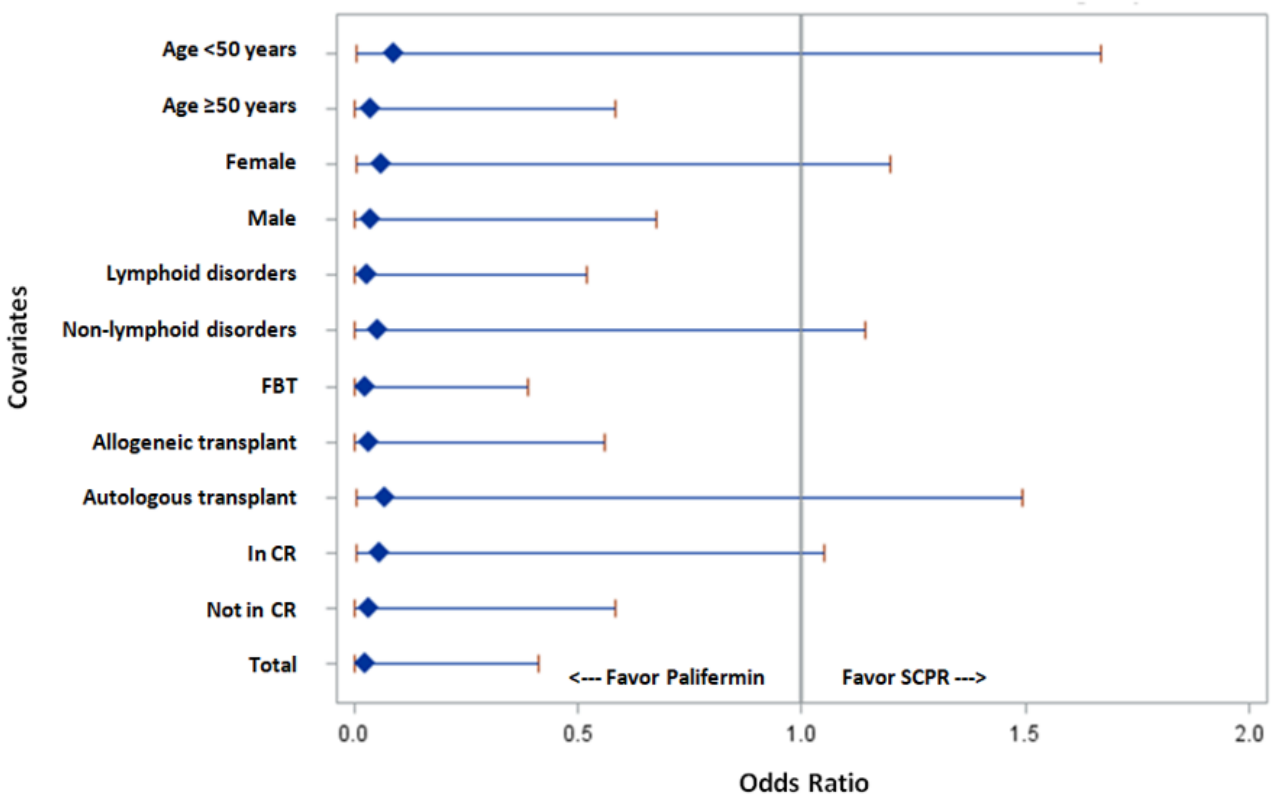

Figure 2

Forest plot showing the prevalence of severe OM among various subgroups