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

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

By

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Master of Public Health

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ABSTRACT

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 OM. However, whether their efficacy differs is unknown.

This study compares SCPR to palifermin in HSCT patients receiving radiotherapy-based myeloablative conditioning. A comprehensive review of our institutional database was performed to identify patients who received myeloablative conditioning therapy between 2008 and 2012. The majority of patients received Fludarabine, Busulfan and total body irradiation.

A total of 26 patients received SCPR and 122 patients received palifermin for OM prophylaxis. Both groups were monitored for development of OM. Multivariable logistic regression analysis was employed to estimate the adjusted odds ratio (aOR) comparing the odds of developing OM between groups and adjusting for age, gender, primary diagnosis, conditioning regimen, donor source and disease status. The odds of developing World Health Organization (WHO) grade 3 or 4 OM were significantly lower in the palifermin group (57% vs 100%, aOR=0.03, p=0.01). Moreover, the palifermin group had lower WHO grade 4 OM (22% vs 62%, aOR=0.19, p=0.0006). The overall odds of developing OM of any grade were not significantly different between the two groups (86% for palifermin group vs 100% for SCPR group, aOR=0.14, p=0.15). Subgroup analyses demonstrated the superiority of palifermin in preventing severe OM, regardless of age, sex, primary diagnosis, donor source, and disease status.

In conclusion, retrospective data suggest that palifermin was more effective than SCPR in preventing severe grades of OM in HSCT patients receiving radiotherapy-based myeloablative conditioning.

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INTRODUCTION AND LITERATURE REVIEW

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) involves infusing stem cells to the patient's circulation after administration of lethal doses of chemotherapy and/or radiation therapy that would otherwise result in permanent bone marrow ablation and severe decrease in circulating blood cells. Infusing these cells results in re-population of the bone marrow cells and restoration of safe level of blood counts (American Society of Addiction Medicine, 2015; Gyurkocza & Sandmaier, 2014; Leukemia and Lymphoma Society, 2015). More than 8,000 patients undergo stem cell transplantation in the United States every year. However, the number seems to be rising, particularly autologous type, most likely brought by the significant decrease in transplant-related morbidity and mortality due to better supportive care and due to availability of innovative sources for stem cells such as umbilical cord and haploidentical transplantation (D'Souza & Fretham, 2017).

Conditioning regimens

Conditioning regimens are combinations of chemotherapy agents with or without total body irradiation (TBI) that are given to the patient before HSCT. The purpose of giving these agents is to eliminate all malignant stem cells that are responsible for the development of the disease being treated. These regimens are often given in high doses, which will likely result in irreversible damage to the healthy stems cells, causing bone marrow aplasia. Prolonged marrow aplasia is associated with multiple complications such as recurrent infections, bleeding and need for frequent blood transfusions (Gill et al., 2010). This complication can usually be minimized if stem cell rescue (from the donor) is administered afterward, a process known as HSCT (Aristei

& Tabilio, 1999; Leukemia and Lymphoma Society, 2015). There are several types of conditioning regimens. High-intensity conditioning regimens that can irreversibly ablate the bone marrow are known as myeloablative regimens. Other conditioning regimens include non-myeloablative regimens, which cause mild decrease of blood count and thus can be given without stem cell support. Another type is reduced-intensity conditioning, which has variable effects on blood count and is usually given with stem cell support but has lower toxicity compared to myeloablative regimens (Bacigalupo et al., 2009).

The process of HSCT

HSCT is a procedure that allows the body to repopulate the bone marrow after eliminating the recipient's malignant cells with the use of conditioning regimens (Leukemia and Lymphoma Society, 2015). Without such a rescue, the high doses of chemotherapy and/or radiotherapy used as conditioning regimens will result in permanent bone marrow aplasia, which often results in death due to fulminant infection or major bleeding. With the use of stem cell rescue, the bone marrow can be repopulated with healthy blood cells, which subsequently prevent infections and bleeding.

Types of HSCT

HSCT is divided based on the source of stem cells. If the source of the stem cells is the patient himself or herself, then HSCT is known as *autologous.* If the donor is an identical twin or triplet, it is known as *syngeneic.* If the donor is another individual, it is known as *allogeneic.* There are several forms of allogeneic HSCT. If the donor is a sibling, then it is known as *matched related donor* HSCT. If the donor is unrelated to the recipient, then it is known as *matched unrelated donor* HSCT. If the donor is half-matched, which is typically seen when the

donor is a family member (e.g. parents, offspring), it is known as *haploidentical* HSCT (Be The Match, 2018). Rarely, stem cells collected from the placenta or the umbilical cord of a newborn are used for HSCT. This type is known as *cord blood* HSCT (American Cancer Society, 2013; American Society of Clinical Oncology, 2016).

Indications for HSCT

Autologous HSCT is used to treat multiple disorders such as certain types of leukemia, various types of lymphoma, multiple myeloma, neuroblastoma, testicular cancers and more recently autoimmune disorders such as multiple sclerosis (American Cancer Society, 2013; Hügle & Daikeler, 2010). Allogeneic HSCT is used to treat aplastic anemia, myelodysplastic syndrome and certain types of leukemia, lymphoma and multiple myeloma. Syngeneic HSCT is rarely performed and is considered when a twin or triplet is available (American Cancer Society, 2013).

Complications of HSCT

HSCT is associated with multiple complications, some of them occur early and others occur late. Early complications occur within the first 100 days of HSCT and include oral mucositis (OM), certain infections, organ injury, graft failure and acute graft-versus-host disease (Miano, Faraci, Dini, & Bordigoni, 2008). Intensive clinical management of early complications has led to lower rate of transplant-related mortality (TRM) (Match, 2016a). Late complications occur after 100 days of HSCT and include certain infections, pulmonary, cardiac and eye complications, secondary cancers and chronic graft-versus-host disease (Match, 2016b; Miano et al., 2008; Socié et al., 2003).

Mucositis

Definition and clinical implications

Mucositis is an inflammatory condition that involves development of ulcerative lesions that can affect any part of the lining of the gastrointestinal tract from mouth to anus (Peterson, Bensadoun, Roila, & Group, 2010). It is one of the most debilitating adverse effects of cancer therapy such as chemotherapy and radiation therapy (Naidu et al., 2004). Oral mucositis (OM) is the most clinically significant form of mucositis due to its major clinical and psychological implications on the affected individuals (Keefe et al., 2007; Tooley, Howarth, & Butler, 2009). These individuals often suffer from severe pain and marked reduction in oral intake, which significantly impairs their nutritional status (Niscola, 2010).

Incidence of OM and its risk factors

Development of OM, particularly severe forms (grade 3 and 4), are related to the type of antineoplastic therapy used, the intensity of therapy and route of administration. When higher doses of radiation therapy are used or when radiation is used concurrently with chemotherapy, the incidence and severity of OM significantly increase (Peterson et al., 2010). In patients receiving radiation therapy for head and neck cancers, OM develops in 91% of patients with 66% develop severe forms of OM (Elting, Cooksley, Chambers, & Garden, 2007). Patients treated for hematological malignancies are at a higher risk for OM, particularly those undergoing HSCT using myeloablative conditioning regimens (Keefe et al., 2007; Niscola, 2010). Without prophylactic therapy, the incidence of severe forms of OM was estimated to be up to 98% in HSCT recipients (Spielberger et al., 2004).

Staging of OM

There are several grading systems for OM. The two most commonly used are the World Health Organization (WHO) grading system and the National Cancer Institute (NCI) grading system.

WHO grading system

The WHO toxicity scale is the most widely used grading system for OM. Accordingly, OM is divided into 5 grades based on involvement of oral mucosa (lining of the mouth). These grades are described below (Miller, Hoogstraten, Staquet, & Winkler, 1981):

- Grade 0: The patient has normal mucosa (no oral ulcers or lesions).
- Grade 1: The patient has erythematous (red) mucosa without swallowing difficulty.
- Grade 2: The patient has oral ulceration with difficulty in swallowing solid but not liquid food.
- Grade 3: The patient has oral ulceration with difficulty in swallowing solid and liquid food.
- Grade 4: The patient has severe ulceration with inability to swallow any food.

NCI grading system

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grades OM depending on oral function. These grades are described below (National Cancer Institute, 2010):

- Grade 1: The patient is asymptomatic or with mild symptoms.
- Grade 2: The patient has moderate pain, but it does not interfere with oral intake.

- Grade 3: The patient has severe pain, which interferes with oral intake.
- Grade 4: The patient has life-threatening consequences related to OM.

OM is typically graded by a health care professional after obtaining history and performing oral examination of the patient.

Pathobiology of OM

The pathobiology of OM is remarkably complex. It was once thought to be secondary to direct mucosal injury inflicted by cytotoxic therapy (M. Dodd, 2004; Sonis et al., 1994; Sonis et al., 2000; Stiff, 2001). The beneficial effect of cryotherapy in preventing high-dose melphalan-induced OM supports this hypothesis. This is because cryotherapy causes vasoconstriction of the blood vessels in the oral cavity, reducing the amount and duration of exposure of oral mucosa to chemotherapy. As a result, the incidence and severity of OM is reduced with cryotherapy (Aisa et al., 2005; Tartarone, Matera, Romano, Vigliotti, & Di Renzo, 2005). Recently, a more complex five-phase model was developed to elucidate the pathogenesis of OM (Sonis, 2009). These phases are: initiation, the primary damage response, signaling and amplification, ulceration, and healing. Additionally, multiple other factors are involved in this process such as transduction and transcription pathways, microbial colonization of the oral cavity and signaling and functional mediators. As a result, OM is considered a dynamic process, which begins with injury and ends with healing.

Prevention of OM

Although several agents and institutional protocols have been used to treat and prevent OM, they are either ineffective or of unconfirmed efficacy (Campbell et al., 2012; M. J. Dodd et

al., 2003; El-Sayed et al., 2002; Niscola, 2010; Pytlik et al., 2002; Stokman et al., 2003). However, there are a few agents that have shown efficacy in preventing OM.

Palifermin

Palifermin is a recombinant keratinocyte growth factor with biologically similar activity to fibroblast growth factor-7 (Beaven & Shea, 2006). The mechanism of action appears to involve stimulation of epithelial proliferation, modulation of clonogenic cell death, and alteration of various cytokines (Blijlevens & Sonis, 2007; Sonis, 2011). 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 recipients receiving chemotherapy with or without TBI (Campbell et al., 2012; Goldberg et al., 2013; Horsley, Bauer, Mazkowiack, Gardner, & Bashford, 2007; Spielberger et al., 2004). Palifermin is administered as two episodes of three consecutive daily doses of 60 µg/kg intravenously given three days before initiation of conditioning and again starting one to two days after HSCT.

SCPR

SCPR is an oral rinse with a high concentration of calcium and phosphorus ions. The exact mechanism of action of SCPR is not known. 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 (M. Markiewicz et al., 2012). SCPR has shown to lower mean measures of oral toxicity, oral pain, and OM duration compared to controls in HSCT recipients receiving conditioning regimens that include chemotherapy with or without TBI (M. Markiewicz et al., 2012; Papas et al., 2003; Wasko-Grabowska et al., 2012). SCPR is

administered at a dose of 71 mg/30 mL four times per day, starting on the day of HSCT and until complete engraftment (improvement of blood count) or resolution of OM (if it has occurred), whichever was later. To date, the efficacy of SCPR has not been compared to palifermin in preventing OM.

Other OM preventive measures

Oral care is usually encouraged in HSCT recipients but has not been proven to prevent OM (McGuire, Correa, Johnson, & Wienandts, 2006). Chlorhexidine digluconate has also not conclusively shown to prevent OM (Stokman et al., 2006). Amifostine is cytoprotective agent that was studied in a single clinical trial and was not beneficial (Buentzel et al., 2006). Glutamine is an amino acid that reduces the production of proinflammitory cytokines. Clinical trials examining its efficacy have been contradictory (Alvariño-Martín & Sarrión-Pérez, 2014). Application of ice to the oral cavity, a procedure known as cryotherapy has shown to reduce the incidence of chemotherapy-induced OM when the chemotherapy used has a short half-life such as melphalan and 5-flurouracil (Lilleby et al., 2006; Svanberg, Birgegard, & Ohrn, 2007). Phototherapy, such as low-level laser therapy has a biomodulating and antiinflammatory effects and has shown to significantly prevent development of OM (Alvariño-Martín & Sarrión-Pérez, 2014; Bjordal et al., 2011). However, due to technical factors, this type of therapy is not widely used.

Treatment of OM

Palifermin

Palifermin is an effective agent in preventing OM (Spielberger et al., 2004). It was approved by the United States Food and Drug Administration for this indication in 2004 (Food

and Drug Administration, 2018). However, it is neither approved nor recommended for treatment of OM (once it has already developed). Animal studies suggest that administration of palifermin after development of OM may even inhibit healing and prolong the duration of ulceration (Dorr, Spekl, & Farrell, 2002).

SCPR

SCPR is usually initiated before development of OM and continued until resolution of ulcerations. Several studies have demonstrated the efficacy of SCPR in preventing OM, reducing the severity of OM once it has developed, reducing OM-associated pain and improving nutritional status (Miroslaw Markiewicz et al., 2012; Quinn, 2013). However, there is no clinical study to date that examined the use of SCPR solely for treatment of OM (i.e. after development of OM).

Supportive measures

Patients with OM suffer significant amount of pain. Therefore, providing the patient with adequate analgesia is key. Saline and topical anesthetic-containing mouthwashes are sometimes used. Nutrition can be severely compromised in patients with OM; therefore, patients should be monitored closely for signs of malnutrition. In addition, the type of diet and route of feeding should be modified depending on the degree of OM. If oral bleeding occurs, topical hemostatic agents may be used. Xerostomia (dry mouth) is frequent in patients with OM and is usually treated by frequent sips of water, using artificial saliva and small amounts of baking soda to keep the oral mucosa adequately moisturized (Lalla, Sonis, & Peterson, 2008).

Oral decontamination

OM has shown to increase the incidence of bacteremia (infection of the blood stream) and, therefore, oral decontamination is recommended to decrease this risk. This includes brushing teeth with a soft toothbrush and flossing. The use of non-medicated rinses such as saline can be helpful as well. Chlorhexidine contains alcohol and is usually poorly tolerated. In addition, it has not been shown to reduce the severity of OM. Therefore, it is not recommended (Barasch, Elad, Altman, Damato, & Epstein, 2006). Although the use of nystatin rinse has not shown to be effective in reducing the severity of OM, the use of systemic fluconazole can lessen the severity of OM-induced by radiation therapy (Epstein, Vickars, Spinelli, & Reece, 1992; Lalla et al., 2008; Nicolatou-Galitis et al., 2006).

Problem statement

It is clear that OM is a common complication of chemotherapy and/or radiotherapy in HSCT recipients. It presents a considerable health burden with remarkable impact on the quality of life of these patients. Therefore, effective intervention is needed to prevent and treat OM in HSCT recipients and even in other cancer patients receiving chemotherapy and/or radiotherapy.

Purpose statement

Prevention is almost always better than cure (Loefler, 2004). As discussed previously, several options are available to prevent OM in HSCT. Palifermin and SCPR have shown clear superiority to usual care in preventing OM in HSCT recipients (Campbell et al., 2012; Goldberg et al., 2013; Horsley et al., 2007; M. Markiewicz et al., 2012; Papas et al., 2003; Spielberger et al., 2004; Wasko-Grabowska et al., 2012). However, to date these agents have not been

compared to each other. In this study, we compared the efficacy of these agents in preventing OM, particularly severe grades. Decreasing the incidence of severe grades of OM would result in better quality of life, less pain, less hospitalization and lower need for parental nutrition (Horsley et al., 2007; Keefe et al., 2007; Niscola, 2010; Tooley et al., 2009)

Research questions

The main question being answered in this study to compare the efficacy of palifermin to SCPR in preventing severe OM. Severe grades of OM (WHO grade 3 and 4) are the most clinically significant OM outcomes and therefore they were chosen. Severe grades of OM are associated with clinically significant pain, dysphagia and have considerable impact on quality of life (Spielberger et al., 2004). Overall odds of developing OM and odds of developing grade 4 OM are chosen as secondary questions. The study was restricted to patients receiving radiotherapy as previous studies suggest different response to OM prophylactic agents based on whether OM is caused by radiotherapy or chemotherapy (Blijlevens et al., 2012; Goldberg et al., 2013).

Significance

OM is a major complication of antineoplastic therapy in HSCT recipients. Effective OM prophylactic agents are desperately needed to improve the outcomes of these patients. OM prophylaxis can decrease the burden of HSCT, which improves the overall outcome and survival of these patients. Selection of which OM prophylactic agent to use in which patient is of an essence to achieve these goals and provide individualized and personalized medical care to HSCT recipients.

Journal selection

The Journal of Community and Supportive Oncology was selected for publication of this article/study. Upon review of multiple journals, it was determined that the focus of this journal aligns well with the focus of this study. Notably, this journal is open-access, peer-reviewed journal with 60% of its readers reported incorporating information they learned from reading its articles into patient care. The journal is indexed in EMBASE, SCOPUS, cumulative index to nursing and allied health literature (CINAHL) and PUBMED.

MATERIALS AND METHODS

Study type

This 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 were tracked for all HSCT recipients.

Study participants

Sample

This study was designed to target subjects who underwent HSCT using a TBI-containing myeloablative conditioning. All patients who fit these criteria at our institution from January 2008 to December 2012 were included in the study. The primary research coordinator at our institution reviewed the institutional database to catalogue the OM prophylactic agent for each

subject. Medical records were also reviewed when necessary. Subjects were divided into two groups; one received SCPR and the other received palifermin. Additionally, institutional database was reviewed to determine the development of OM and the documented grade of OM.

Inclusion criteria

All patients who received TBI-containing myeloablative conditioning during the study period were included in this study. All patients were de-identified.

Exclusion criteria

Any patient who received no agent to prevent OM or received conditioning regimens that did not contain TBI was excluded from the study.

HSCT process

Coding of HSCT

We will call the day of HSCT *day 0*. Each day after the day of HSCT and moving forward will be called in (positive) numeric order. For example, the day after the day of HSCT is called *day 1* and the second day after the day of HSCT is called *day 2* and so forth. On the other hand, the days before the day HSCT are counted starting at the day of HSCT (*day 0*) and moving backward with the minus sign. For example, the day before the day of HSCT is called *day -1* and the day that is 2 days before the day of HSCT is called *day -2* and so forth.

Conditioning regimens

All subjects in the study received conditioning regimens. Although all subjects in the study received TBI, the chemotherapy agents varied between subjects. However, the most

common conditioning regimen used was Fludarabine and Busulfan in addition to low dose TBI (FBT). Fludarabine was administered intravenously at a dose of 50 mg/m^2 daily for 5 consecutive days (days -6 to -2, inclusive). Busulfan was administered intravenously at a dose of 3.2 mg/kg of adjusted body weight daily for 4 days (days -5 to -2, inclusive). TBI was administered at a dose of 200 cGy daily for 2 consecutive days (days -1 and 0), when administered as part of FBT regimen.

When used, Cyclophosphamide was administered at a dose of 60 mg/kg daily for 2 days. Etoposide is 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.

The majority of the patients in this study received FBT conditioning regimen. The other less commonly used regimens were Fludarabine, Cyclophosphamide and TBI (FCT), Cyclophosphamide and TBI (CT) and Etoposide (also known as VP16) and TBI (VT).

Study drugs

SCPR was administered at a dose of 71 mg/30 mL four times per day, starting on the day of HSCT and until full engraftment (improvement of the blood cell counts) or resolution of OM, whichever was later (EUSAPharma, 2018). 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 (Spielberger et al., 2004). 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. Cryotherapy (applying ice to oral mucosa), a method occasionally use to prevent OM, was not used in this study.

Study outcomes

The primary aim of this study is to compare palifermin to SCPR in reducing the odds of developing grade 3 or grade 4 OM. The secondary outcomes are to compare palifermin to SCPR in reducing the overall incidence of all OM grades. Another secondary outcome is to compare palifermin to SCPR in reducing the incidence of grade 4 OM. We also assessed whether age, sex, primary diagnosis, donor type or disease status are associated with development of severe OM (grade 3 and 4). Finally, we also assessed if the efficacy of either agent is superior in specific subsets of patients stratified by age, gender, primary diagnosis, donor type and disease status.

Assessment of outcome

As part of the institutional procedure, patients were assessed daily for the development and severity of OM by an experienced transplant physician beginning on the day of transplantation (day 0) and continuing until neutrophil engraftment (improvement of blood count) or resolution of OM, whichever was later. OM was graded according to the five-grade WHO toxicity scale (Miller et al., 1981). Details of the WHO toxicity scale for OM are discussed in detail in the "introduction and literature review>Mucositis>staging of OM" section. This information was stored in an institutional database to assist in tracking the outcomes of the transplant center and to provide basis for quality improvement. Fortunately, this information was available for extraction for research purposes after institutional review board (IRB) approved this study and was thus used 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 for herpes zoster virus prophylaxis starting 3 days before initiation of conditioning therapy and continued for at least 2 years after HSCT (Yahav et al., 2009).

Statistical analysis

All datapoints and variables were reviewed and organized for analysis. The baseline characteristics of subjects were categorized (when appropriate) and compared between groups (palifermin group and SCPR group) using the Student's *t*-test for continuous variable (age) and *chi*-square or Fisher's exact test for categorical variables (gender, primary diagnosis, conditioning regimen, donor type, disease status). The overall odds of OM, odds of severe OM (grade 3 and 4), and odds of grade 4 OM were estimated using logistic regression. Estimates were calculated using odds ratio (OR). An unadjusted analysis was performed initially and then a multiviariable analysis was conducted to adjust for possible confounding. When convergence failed due to complete or quasi-separation, Firth estimation was employed. Cochran-Armitage trend test was used to compare the trend of OM grades between the groups. Multivariable analyses were conducted to identify predictors of OM and its severe forms (i.e. grade 3 and 4 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 and secondary outcomes. All tests used were two-sided. A significance level of 0.05 was used.

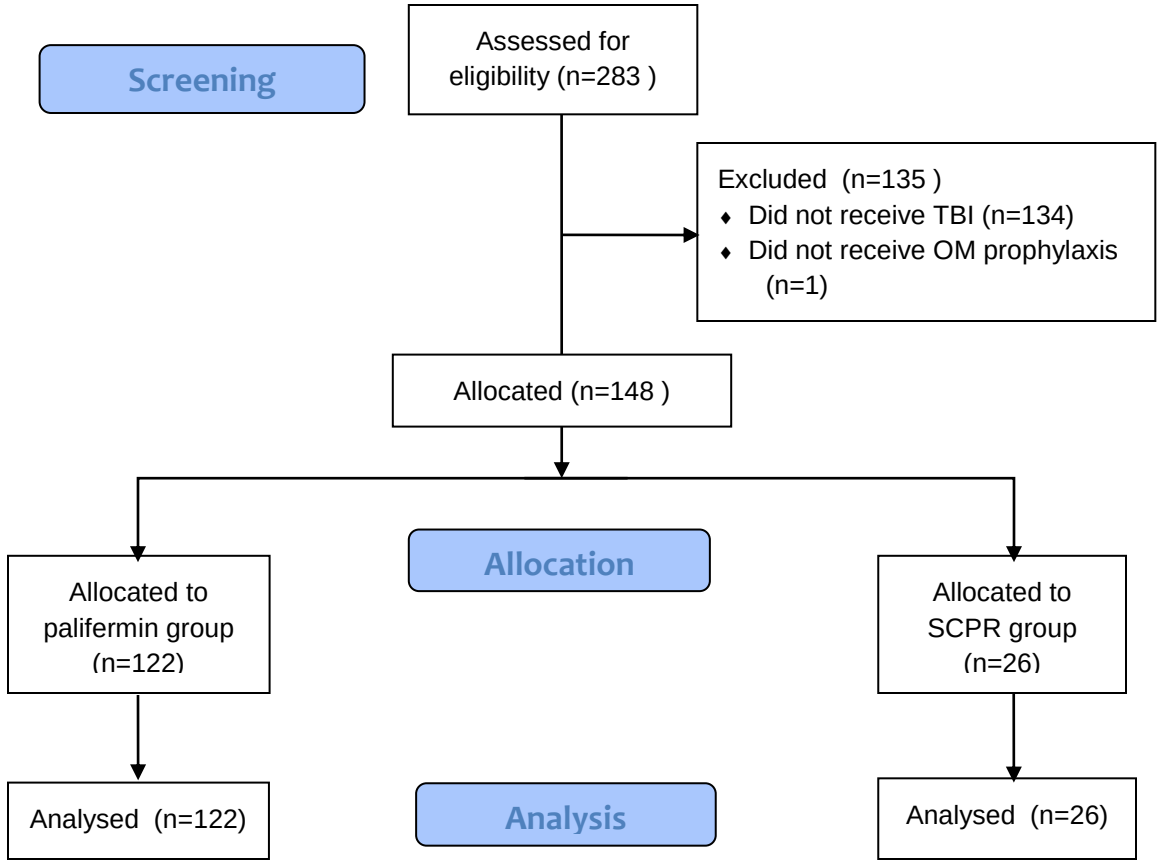
Ethical considerations

This study was submitted to the IRB and determined to be "exempt" both at the primary institution and Emory University.

RESULTS

A total of 149 patients underwent TBI-containing HSCT between 2008 and 2012 at the Western Pennsylvania Hospital in Pittsburgh, PA. One patient was excluded as no OM prophylactic agent was used. Among the remaining patients, 26 subjects received SCPR and 122 received palifermin (Figure 1).

Figure 1: CONSORT flow diagram



Baseline characteristics of the subjects are summarized in Table 1. These characteristics were similar between the two groups in regard to age, gender, conditioning regimen, donor source and disease status. Numerically, there was a higher percentage of subjects with lymphoid disorders in the SCPR group and a higher percentage of subjects with myeloid disorders in the palifermin group. However, these were significantly different between the two groups (Table 1).

Table 1: Patients' characteristics compared between the two groups

Variable	SCPR[a] group N=26	Palifermin group N=122	p-value
Age-years			0.78
Mean ± SD[b]	51±13.9	50 ±12.6	
Range	(23-68)	(20-74)	
Male – n (%)	15 (58)	67 (55)	0.80
Female – n (%)	11 (42)	55 (45)	
Diagnosis – n (%)			0.1
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 (%)			0.31[g]
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)	Ref
Allogeneic	18 (69)	72 (59)	0.33
Umbilical cord	0 (0)	8 (7)	0.21[g]
Disease Status – n (%)			0.68
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, [g]Fisher exact test was used.

Efficacy

The efficacy of OM prophylaxis was calculated for primary and secondary outcomes and is summarized in Table 2a and Table 2b.

Odds of developing severe OM

In the palifermin group, 69 subjects (57%) developed severe OM compared to 26 (100%) in the SCPR group. After adjusting for age, gender, diagnosis, conditioning regimen, donor source and disease status, the odds of developing severe OM were significantly lower in the palifermin group (aOR=0.03, p=0.01, 95% CI=0.002 to 0.41).

Incidence of grade 4 OM

In the palifermin group, 27 subjects (22%) developed grade 4 OM compared to 16 (62%) in the SCPR group. After adjusting for age, gender, diagnosis, conditioning regimen, donor source and disease status, the odds of developing grade 4 OM were significantly lower in the palifermin group (aOR=0.19 p=0.0006, 95% CI=0.07 to 0.49).

Incidence of all-grade OM

In the palifermin group, 105 subjects (86%) developed all-grade OM compared to 26 (100%) in the SCPR group. The overall odds of developing OM were numerically lower in the palifermin group. After adjusting for age, gender, diagnosis, conditioning regimen, donor source and disease status, the odds radio were not significantly different from 1 (aOR=0.14, p=0.15, 95% CI=0.009 to 2.08).

Table 2a: Development and severity of oral mucositis (unadjusted analysis)

Variable	Palifermin group N=122	SCPR[a] group N=26	Unadjusted OR[b]	p-value	95% CI[c] for OR (Palifermin vs SCPR)
Overall odds of developing OM – n (%)	105 (86)	26 (100)	0.114	0.14	0.006 to 2.06[d]
Odds of developing WHO[d] grade 3/4 – n (%)	69 (57)	26 (100)	0.024	0.01	0.001 to 0.43[d]
Odds of developing WHO grade 4 – n (%)	27 (22)	16 (62)	0.178	0.0002	0.07 to 0.44

[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

Table 2b: Development and severity of oral mucositis (adjusted analysis)

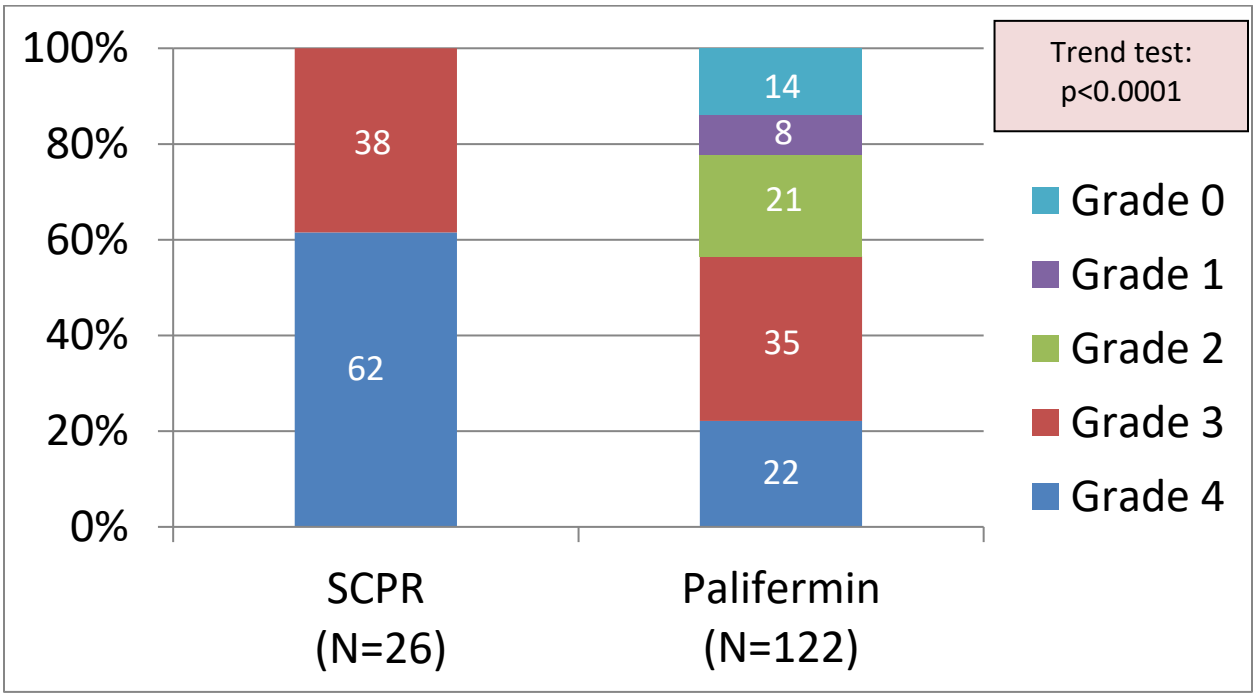
Variable	Palifermin group N=122	SCPR[a] group N=26	Adjusted OR[b]	p value	95% CI[c] for OR (Palifermin vs SCPR)
Overall odds of developing OM – n (%)	105 (86)	26 (100)	0.136	0.15	0.009 to 2.08[d]
Odds of developing WHO[d] grade 3/4 – n (%)	69 (57)	26 (100)	0.026	0.01	0.002 to 0.41[d]
Odds of developing WHO grade 4 – 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.

Distribution of OM

The overall distribution of grades of OM is depicted in Figure 2. There is a statistically significant trend toward lower grade of OM among the palifermin group (p<0.0001).

Figure 2: Distribution of OM in the two groups (%)



Prediction of severe OM

Multivariable analyses were conducted to predict the impact of various variables on the occurrence of severe OM. Variables included in the analyses were age, gender, primary diagnosis, donor type, and disease status at the time of HSCT. None of these variables were predictive of occurrence of severe grades of OM (Table 3). This explains the minor difference in the values of the estimates when calculated using unadjusted and adjusted analyses.

Table 3: Prediction of severe OM using various variables (adjusted analysis)

Variable	aOR[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** **UC[e] vs autologous**	0.87 4.19	0.78 0.2	0.33-2.27 0.47-37.16
Disease Status - (in CR[f] vs not in CR)	1.28	0.54	0.58-2.83

[a]aOR: Adjusted odds ratio, [2]CI: Confidence interval, [c]SCPR: Supersaturated calcium phosphate rinse, [d]FBT: Fludarabine, busulfan and TBI, [e]UC: Umbilical cord, [f]Complete remission. All estimates of this variable were calculated using the firth method.

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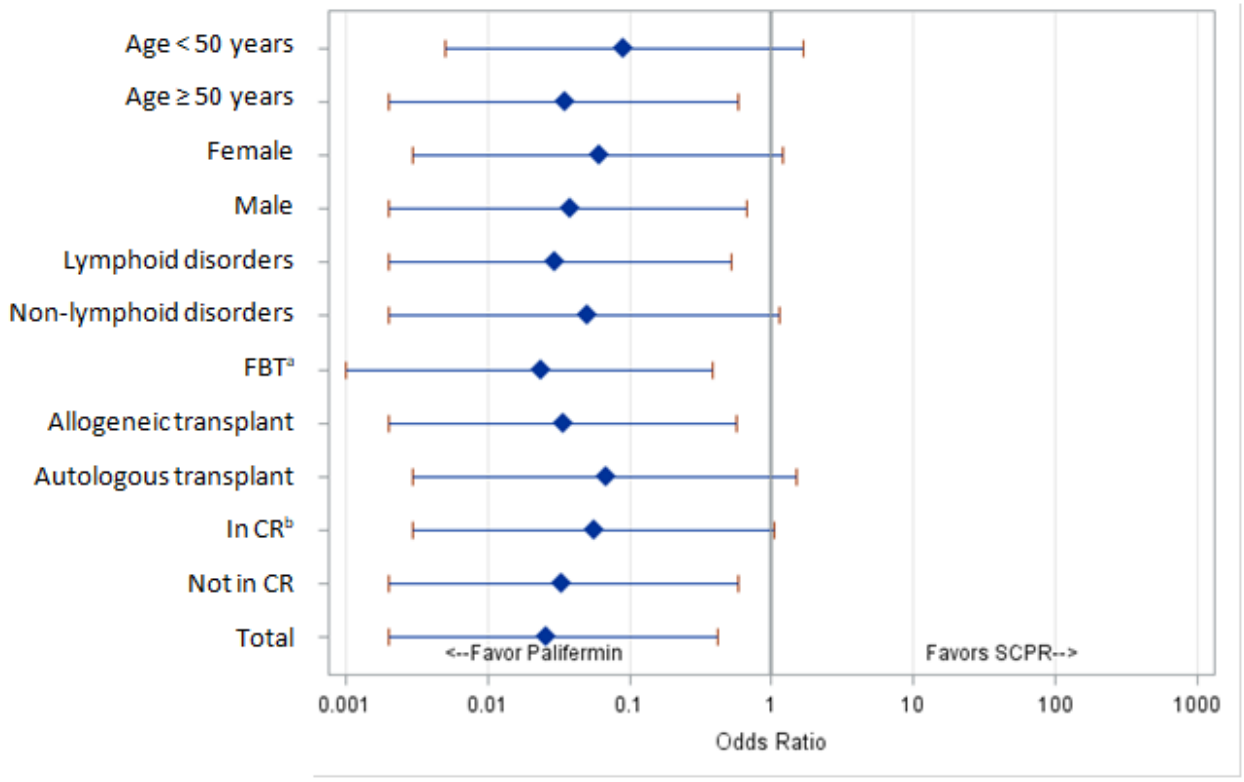
Subgroup analysis

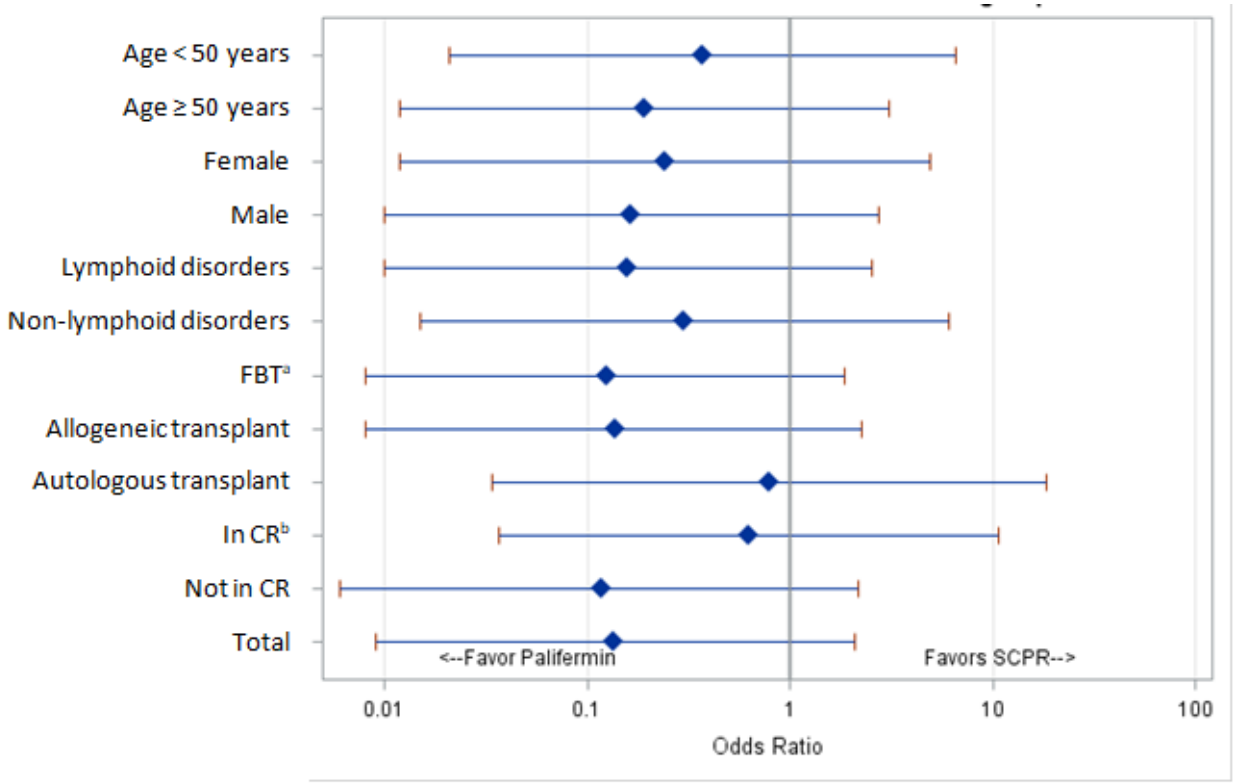
The data was analyzed using various subgroups. After adjusting for age, gender, diagnosis, conditioning regimen, donor source and disease status, there was a consistent trend toward lower overall odds of developing OM and severe OM with the use of palifermin among various groups (Figure 3a and Figure 3b)

Figure 3a: Forest plot showing the odds of developing severe OM among various subgroups (logarithmic scale is used)



[a]FBT: Fludarabine, busulfan and TBI, [b]CR: Complete remission.

Figure 3b: Forest plot showing the overall odds of OM among various subgroups (logarithmic scale is used)



[a]FBT: Fludarabine, busulfan and TBI, [b]CR: Complete remission.

DISCUSSION

Palifermin is a recombinant keratinocyte growth factor with biologically similar activity to fibroblast growth factor-7 (Beaven & Shea, 2006). The mechanism of its action appears to involve stimulation of epithelial proliferation, modulation of clonogenic cell death, and alteration of various cytokines (Blijlevens & Sonis, 2007; Sonis, 2011). SCPR is an oral rinse with a high

concentration of calcium and phosphorus ions. While its exact mechanism of action in OM is not known, it is thought to play a major role in intracellular signaling, inflammation, and mucosal repair (M. Markiewicz et al., 2012). Previous studies have demonstrated the superiority of both palifermin and SCPR to placebo in reducing the severity and duration of OM and oral pain in HSCT patients receiving chemotherapy with or without TBI (Campbell et al., 2012; Goldberg et al., 2013; Horsley et al., 2007; M. Markiewicz et al., 2012; Papas et al., 2003; Spielberger et al., 2004; Wasko-Grabowska et al., 2012). Yet, palifermin has not been compared to SCPR. In this study, administration of palifermin resulted in a notable reduction in the odds of developing severe grades of 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 or no 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 with only a minority received TBI in combination with other chemotherapeutic agents at doses known to cause severe mucositis. Notably, the odds of developing grade 3 and 4 mucositis among patients who received SCPR in our study (100%) is comparable to the previously reported incidence when placebo is used (Spielberger et al., 2004), which suggests the ineffectiveness of SCPR in preventing OM in our patient population. Of interest, recently published studies showed that palifermin may have limited efficacy in chemotherapy-induced OM, particularly in high-dose melphalan-induced OM (Blijlevens et al., 2012; Goldberg et al., 2013). This may suggest that palifermin may be particularly effective in radiotherapy-induced OM. Thus, the optimal prophylaxis for chemotherapy- induced OM remains unclear.

A complex five-phase model was recently developed to explain the pathogenesis of OM (Sonis, 2009). However, this model continues to view OM as a universal outcome regardless of the causative agent. The differential benefit of palifermin in radiotherapy-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 (Hahn et al., 2010; Sonis, 2011). Palifermin is thought to exert its OM prophylactic effect through this pathway, which may explain the efficacy of palifermin over SCPR in radiotherapy-induced mucosal injury (Blijlevens & Sonis, 2007; Sonis, 2011).

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 (age, gender, diagnosis, donor source and disease status) proved to be predictive of the severity of OM, except the type of prophylactic agent employed. This suggests that OM occurs predominantly due to the causative agents (conditioning therapy) with little influence from host factors. However, 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 (Hahn et al., 2010; Sonis, 2011). If replicated, this may present an attractive method to predict development 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 $20.3. Therefore, the cost of palifermin for a 70kg patient is estimated to be $10,250 (Center for Medicare and Medicaid, 2018). A 30 day supply of SCPR has a retail cost of $824.55 (GoodPx, 2018).

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 nonsignificant 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 (Elting, Shih, et al., 2007). Nonetheless, whether palifermin will continue to be cost-saving or cost-effective when compared to SCPR remains uncertain.

Limitations

There are several limitations with this study. First, the majority of our patients received lower dose TBI (400 cGy) than used in most other studies. Nonetheless, the odds of developing grade 3 or 4 OM in our patients was 57%, which is comparable to the incidence of 63% reported with TBI dosing of 1200 cGy (Sonis, 2009). Moreover, the retrospective design of our study and policy-driven selection of OM prophylactic therapy may be susceptible to bias. Prophylactic therapy was administered according to institutional protocols extant during the time period 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, this study evaluated the incidence and severity of OM but not oral pain, analgesic use, use of parenteral nutrition, systemic infection, length of hospital stay, 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.

Implications on public health

There is a notable advancement in medical therapy within the last decade. While HSCT remains an integral part of management of several malignant conditions, improving supportive therapy is key in order to improve survival and quality of life of these patients and decrease treatment-related mortality. This is particularly important in countries with limited resources where there is a desperate need to use these resources to treat as many individuals as possible. Therefore, selecting the most cost-effective/cost-saving resources for the patient most likely to benefit from these modalities is key to allow optimal and more widespread utilization of these resources.

Conclusions and future directions

This retrospective study suggests that palifermin is more effective than SCPR in reducing the severity of OM in patients conditioned with TBI-containing myeloablative therapy. Based on this study and others, palifermin is a reasonable effective option for prophylaxis against OM in HSCT subjects receiving myeloablative TBI-containing conditioning therapy. Ideally, a randomized study would confirm our conclusions. Further studies are needed to determine the optimal OM prophylactic strategy in TBI-containing and non-TBI-containing conditioning regimens and identify potential predictors of OM. Additionally, studies focusing on countries with limited resources may be helpful to facilitate more widespread use of cost-effective and cost-saving medical care.

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APPENDIX:

SAS codes:

```
*Making library name;

libname thesis "H:/";


*changing excel file to SAS;

proc import datafile="C:\Users\thadid\Desktop\Tarik1.xlsx"

out=Tarik1

DBMS = excel

replace;

run;


*Printing data;

proc print data=Tarik1;

run;


*Sorting by PAL;

proc sort data= tarik1;

by PAL;

run;


*Categotizing dx;

data tarik2;
```

```
set tarik1;
if dx ="AML" then dxx =0;
else if dx ="CML" then dxx =0;
else if dx ="MDS" then dxx=0;
else if dx ="MPN" then dxx=0;
else if dx ="NHL" then dxx=1;
else if dx="MHL" then dxx=1;
else if dx ="HL" then dxx=1;
else if dx ="CLL" then dxx=1;
else if dx ="ALL" then dxx=1;
else if dx ="MM" then dxx=2;
else dxx=3;
run;

proc print data=tarik2;
run;

*deleting empty cells;
data tarik3;
set tarik2;
if ID=. then delete;
run;
```

```
*Changing PAL to yes and no;

data tarik3;

set tarik3;

if PAL= "Yes" then PAL=1;

else PAL=0;

if id =. then delete;

drop comment;

run;


proc print data=tarik3;

run;


*making female variable;

data tarik3;

set tarik3;

if gender="F" then female =1;

else female=0;

run;


proc freq data=tarik3;

tables gender*female;

run;
```

```
*Changing transplant type to dummy variables;

data tarik4;

set tarik3;

if transplant_type ="AUTO" then transplant="AUTO";

else if transplant_type ="ALLO" then transplant="ALLO";

else if transplant_type ="MUD" then transplant="ALLO";

else transplant ="UC";


run;


*Changing disease_status to CR yes or no;

data tarik5;

set tarik4;

if disease_status ="CR" then cr=1; else cr=0;

run;


*frequency tables;

proc freq data =tarik5;

tables (gender transplant dxx cr tx)* pal / chisq fisher;

run;


*Making nonlymphoid category of dxx (diagnosis);

data tarik5e;
```

```
set tarik5;
if dxx = 1 then lymphoid=1;
else lymphoid=0;
run;

*MAKING FBT in tx category (conditioning regimens);
data tarik5ee;
set tarik5e;
if tx="FBT" then FBT=1;
else FBT=0;
run;

proc freq data=tarik5ee;
tables FBT*pal;
run;

*Making dummy variables for Transplant (donor);
data tarik5eee;
set tarik5ee;
if transplant="ALLO" then allo=1;
else allo=0;
if transplant="UC" then UC=1;
else UC=0;
```

```
run;

proc freq data=tarik5eee;
tables (allo UC)*transplant;
run;

*making OM outcome variable;
data Tarik5eee;
set tarik5eee;
if muco =0 then OM=0;
else OM=1;
run;

*making OM outcome variable;
data Tarik6;
set tarik5eee;
if muco =0 then severeOM=0;
else if muco=1 then severeOM=0;
else if muco=2 then severeOM=0;
else severeOM=1;
run;

proc freq data=tarik6;
```

```
tables muco*OM;

run;


proc freq data=tarik6;

tables muco*severeOM;

run;


*Making grade4 category;

data tarik6;

set tarik6;

if muco=4 then grade4=1;

else grade4=0;

run;


proc freq data=tarik6;

tables muco*grade4;

run;


******ANALYSIS******


*TABLE 1;


*age ttest;
```

```
proc ttest data = tarik6;
class pal;
var age;
run;


*chi sq test for transplant caregories (allo, UC) and conditioning regimen (FBT) and diagnosis
(lymphoid);
proc freq data =tarik6;
tables (gender lymphoid FBT allo UC cr)*pal /chisq fisher;
run;

**OUTCOME DATA**
*Unadjusted primary outcome;

*freq table;
proc freq data=tarik6;
tables SevereOM * PAL;
run;

*unadjusted logistic regression, primary outcome;
proc logistic data = tarik6 descending;
class PAL (ref="0");
```

```
model SevereOM (ref = "0") = PAL  / firth cl;
run;

*unadjusted logistic regression, secondary outcome;
proc logistic data = tarik6 descending;
class PAL (ref="0");
model OM (ref = "0") = PAL  / cl;
run;

*unadjusted logistic regression, grade 4;
proc logistic data = tarik6 descending;
class PAL (ref="0");
model Grade4 (ref = "0") = PAL  /cl;
run;

*adjusted logistic regression, primary outcome;
proc logistic data = tarik6 descending;
class PAL (ref="0");
model SevereOM (ref = "0") = PAL age female lymphoid  FBT allo UC cr / firth cl;
run;

*adjusted logistic regression, secondary outcome;
```

```
proc logistic data = tarik6 descending;
class PAL (ref="0");
model OM (ref = "0") = PAL age female lymphoid  FBT allo UC cr / firth cl;
run;

*adjusted logistic regression, grade4;
proc logistic data = tarik6 descending;
class PAL (ref="0");
model grade4 (ref = "0") = PAL age female lymphoid  FBT allo UC cr / cl;
run;

*Distribution/Frequency of grades of OM;
proc freq data =tarik5;
tables muco* pal / chisq fisher trend;
run;

***SUBGROUP ANALYSIS***
*subgroup model for primary outcome;
*Age;
data tarik7;
set tarik6;
if age >49 then more49=1;
else more49=0;
```

```
run;

*model SevereOM age >49;
proc logistic data = tarik7 descending;
where more49 = 1;
class pal (ref = "0");
model SevereOM (ref = "0") = pal female lymphoid FBT allo UC cr/ firth cl;
run;
*Model SevereOM age =<49;
proc logistic data = tarik7 descending;
where more49 = 0;
class pal (ref = "0");
model SevereOM (ref = "0") = pal female lymphoid FBT allo UC cr/ firth cl;
run;

*Model SevereOM female Gender;
proc logistic data = tarik7 descending;
where female=1;
class pal (ref = "0");
model SevereOM (ref = "0") = pal age lymphoid FBT allo UC cr/ firth cl;
run;

*Model SevereOM male gender;
```

```
proc logistic data = tarik7 descending;
where female=0;
class pal (ref = "0");
model SevereOM (ref = "0") = pal age lymphoid FBT allo UC cr/ firth cl;
run;

*Model SevereOM lymphoid dz;
proc logistic data = tarik7 descending;
where lymphoid =1 ;
class pal (ref = "0");
model SevereOM (ref = "0") = pal age female FBT allo UC cr/firth cl;
run;

*Model SevereOM for non-lymphoid dz;
proc logistic data = tarik7 descending;
where lymphoid =0 ;
class pal (ref = "0");
model SevereOM (ref = "0") = pal age female FBT allo UC cr/firth cl;
run;

*Model SevereOM for FBT;
proc logistic data = tarik7 descending;
where FBT=1;
```

```
class pal (ref = "0");
model SevereOM (ref = "0") = pal age female lymphoid allo UC cr/firth cl;
run;

*Model for SevereOM for allo;
proc logistic data = tarik7 descending;
where allo =1 ;
class pal (ref = "0");
model SevereOM (ref = "0") = pal age female lymphoid FBT cr/firth cl;
run;

*Model SevereOM for auto;
proc logistic data = tarik7 descending;
where allo=0 and UC=0;
class pal (ref = "0");
model SevereOM (ref = "0") = pal age female lymphoid FBT cr/firth cl;
run;

*Model SevereOM in CR;
proc logistic data = tarik7 descending;
where CR = 1;
class pal (ref = "0");
model SevereOM (ref = "0") = pal  age female lymphoid FBT allo UC/ firth cl;
```

```
run;

*Model SevereOM no CR;
proc logistic data = tarik7 descending;
where CR = 0;
class pal (ref = "0");
model SevereOM (ref = "0") = pal  age female lymphoid FBT allo UC/ firth cl;
run;

*Model SevereOM total;
proc logistic data = tarik7 descending;
class pal (ref = "0");
model SevereOM (ref = "0") = pal  age female lymphoid FBT allo UC CR/ firth cl;
run;

*Forest for severe OM- subgroup analysis;
data forest1;

input Subgroup $ group $ OddsRatio LowerCL UpperCL;


datalines;
Total 2 0.026 0.002 0.413
```

```
Not_CR 1 0.033 0.002 0.584
In_CR 1 0.056 0.003 1.050
Auto 1 0.068 0.003 1.492
Allo 1 0.034 0.002 0.561
FBT 1 0.024 0.001 0.387
Nonlymph 1 0.051 0.002 1.142
Lymphoid 1 0.030 0.002 0.519
Male 1 0.038 0.002 0.677
Female 1 0.061 0.003 1.197
Age>=50 1 0.035 0.002 0.585
Age<50 1 0.090 0.005 1.667
;
run;
title "Incidence of Severe Oral mucositis in Various Subgroups";
proc sgplot data =forest1 noautolegend nocycleattrs;
refline 1  / lineattrs=(thickness=2) transparency=0 axis=x;
scatter x =Oddsratio y=Subgroup /xerrorlower=LowerCL xerrorupper=UpperCL
                        markerattrs= Addsratio(symbol=DiamondFilled size= 10);
highlow y=subgroup low=LowerCL high=UpperCL / type=line;

refline 1 100 / axis=x;

inset "                              <--Favor Palifermin" / position=bottomleft;
```

```
 inset "Favors SCPR-->                                    "  / position=bottomright;
xaxis grid type=log label="Odds Ratio" min=0.001 max =1000;

yaxis label="Covariates";
run;


 *Forest for OM- subgroup analysis;


data forest2;
input Subgroup $ group $ OddsRatio LowerCL UpperCL;



datalines;
Total 2 0.136 0.009 2.077
Not_CR 1 0.118 0.006 2.184
In_CR 1 0.629 0.037 10.614
Auto 1 0.790 0.034 18.510
Allo 1 0.138 0.008 2.257
FBT 1 0.124 0.008 1.878
Non-Lymph 1 0.300 0.015 6.034
Lymphoid 1 0.157 0.010 2.552
Male 1 0.164 0.010 2.766
Female 1 0.241 0.012 4.887
Age=50 1 0.191 0.012 3.069
```

```
Age<50 1 0.368 0.021 6.580


;

run;


title "Overall Incidence of Oral mucositis in Various Subgroups";

proc sgplot data =forest2 noautolegend nocycleattrs;

refline 1  / lineattrs=(thickness=2) transparency=0 axis=x;

scatter x =Oddsratio y=Subgroup /xerrorlower=LowerCL xerrorupper=UpperCL

                        markerattrs= Addsratio(symbol=DiamondFilled size= 10);

highlow y=subgroup low=LowerCL high=UpperCL / type=line;



inset "                              <--Favor Palifermin" / position=bottomleft;

 inset "Favors SCPR-->                                  "  / position=bottomright;

xaxis grid type=log label="Odds Ratio" min=0.001 max =1000;


yaxis label="Covariates";

run;
```