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REVIEW

# Efficacy of palifermin (keratinocyte growth factor-1) in the amelioration of oral mucositis

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**Purpose:** Oral mucositis is a significant toxicity of cytotoxic chemo- and radiation-therapy used to treat cancer. Palifermin is the first pharmaceutical/biological agent approved for the intervention of oral mucositis. The major objective of this review is to evaluate the evidence supporting the use of palifermin.

**Methods:** A literature search was performed using an appropriate keyword search in MEDLINE and PubMed databases.

**Results:** Of 100 full papers and 4 abstracts identified, 12 papers and 3 abstracts were appropriate for analysis. Level 2 evidence supporting palifermin use in patients with hematologic malignancies being treated with autologous hematopoietic stem cell transplantation (HSCT) is clear. Level 2 evidence also exists for the use of palifermin in the prevention of oral mucositis in patients with solid tumors (colorectal cancer, head and neck cancer), but is incomplete. Level $\geq 3$ data support the use of palifermin in allogeneic HSCT recipients and cycled chemotherapy. A single health economic study concluded that palifermin is essentially cost neutral in the autologous HSCT population.

**Conclusion:** Data supporting the use of palifermin in autologous HSCT recipients with hematologic malignancies is clear. Some data exist demonstrating its efficacy in other oncologic indications. Additional studies are needed to broaden the potential applications of palifermin and to ascertain its economic, but not symptomatic, effectiveness.

**Keywords:** oral mucositis, palifermin, toxicity

**Core evidence proof of concept summary for palifermin in the amelioration of oral mucositis**

| Outcome measure | Evidence | Implications |
|---|---|---|
| Patient-oriented evidence | | |
| Reduced incidence of severe oral mucositis in autologous HSCT recipients | Clear | Reduced need for opioid analgesics |
| Reduced duration of severe oral mucositis in autologous HSCT recipients | Clear | Reduced need for opioid analgesics |
| | | Reduced risk of febrile neutropenia |
| | | Reduced need for TPN |
| | | Patient-reported function improved |
| | | Reduced hospital stay |

(*Continued*)

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(*Continued*)

| Outcome measure | Evidence | Implications |
|---|---|---|
| Reduced incidence of ulcerative oral mucositis in allogeneic HSCT recipients | Some | As above |
| Reduced duration of ulcerative oral mucositis in allogeneic HSCT recipients | Some | As above |
| Reduced incidence of ulcerative oral mucositis in patients receiving cycled chemotherapy | Some | Reduced need for chemotherapy dose reductions |
| | | Reduced patient-reported mucositis associated symptoms |
| Reduced time to onset, duration, and incidence of ulcerative oral mucositis in patients receiving chemoradiation for cancers of the head and neck | Some | Reduced breaks in radiotherapy or chemotherapy |
| | | Reduced analgesic use |
| | | Reduced reliance on gastrostomy tube feedings |
| | | Fewer unplanned office and emergency room visits and hospital admission |
| **Economic evidence** | | |
| Cost-effective in reducing costs associated with mucositis-associated complications in autologous | | Reduction in mucositis-associated adverse outcomes offset cost of palifermin. |
| HSCT recipients | | Nonsignificant savings (US$3,595) per patient |

**Abbreviations:** HSCT, hematopoietic stem cell transplantation.

## Scopes, aims, and objectives

Oral mucositis is a significant and common toxicity of both drug and radiation therapy used for the treatment of many cancers. In some cases, its severity limits patients' ability to tolerate and continue cancer therapy. The lack of an effective intervention has frustrated patients and their healthcare providers since the advent of cytotoxic cancer treatment. Recently palifermin (Kepivance®) became the first pharmaceutical/biological approved for the treatment of mucositis, although in a small segment of the at risk population. The main objective of this article is to evaluate the evidence supporting the use of palifermin for its approved indication in patients undergoing hematopoietic stem cell transplantation (HSCT) for hematologic maligancies, and for other populations at risk of oral mucositis. Additional discussion will assess studies assessing the cost-effectiveness of palifermin.

## Methods

Data were obtained with an online search strategy of MEDLINE and PubMed databases using the following search terms: 'palifermin', 'keratinocyte growth factor (KGF)', and 'mucositis'. In addition, meeting abstracts for American Society of Clinical Oncology (ASCO) and American Society for Therapeutic Radiology and Oncology (ASTRO) were searched using the keywords 'mucositis' and 'palifermin'.

The selection of papers and abstracts for inclusion was limited to human clinical trials. Reviews and pre-clinical studies were excluded.

## Disease overview

Oral mucositis is a common, painful, debilitating toxicity of many forms of chemotherapy and radiation to the head and neck.[1] The condition results in a continuum of clinical changes that range from erythema and burning of the oral and oropharyngeal mucosa to the development of diffuse and confluent ulcerations. The latter are often of such severity as to require opioids to manage pain, inhibit eating or drinking so necessitating parenteral nutrition, cause unscheduled office and emergency room visits, and hospital admission for fluid support. In patients who are myeloablated, mucosal ulcerations result in a conduit for oral bacteria to enter the bloodstream and cause bacteremia and sepsis. Because of its

severity, mucositis is a common reason for compromising modifications in dosing or treatment schedules which adversely impact tumor outcome.

The incidence and severity of mucositis is determined by a number of factors including cancer diagnosis, drug choice and dose, drug or radiation schedule, patient age, body mass, and gender, and a range of genetic factors. Among patients being treated with concomitant chemoradiation for cancers of the head and neck, the incidence of severe mucositis exceeds 50%. Almost all patients being treated for cancers of the mouth and oropharynx will develop severe ulcerative lesions. Patients receiving aggressive myeloablative chemotherapy as part of conditioning regimens preceding HSCT, especially regimens in which total body irradiation (TBI) is given are also at particularly high (>50%) risk of severe mucositis.

Mucositis risk varies among patients with colorectal or breast cancers who receive multicycle chemotherapy. Although the reported cycle 1 incidence varies, about 20% of patients being treated with commonly used chemotherapy regimens for either of the above cancers reportedly develop ulcerative oral mucositis. This risk increases with subsequent cycles if no adjustment in dose (dose de-escalation) is made.

It is noteworthy that the incidence and severity of oral mucositis, like the majority of toxicities, is underreported. This discrepancy was clearly illustrated in the results of a recent study of colorectal patients in which over 70% of patients reported symptoms of mucositis, a much higher number than expected based on literature reports.[2]

It has been estimated that there will be about 450,000 patients affected by oral mucositis in the United States this year. The incremental cost of the condition appears to be significant. Among a population of patients with non-small cell lung or head and neck cancers, Nonzee and colleagues reported a differential cost between patients with mucositis compared to those without the condition of US$18,515 (US$39,313 with mucositis vs $20798 without mucositis).[3] As noted by Sonis and colleagues, a similar trend was seen in patients receiving HSCT where an increase in mucositis severity as expressed by a one-point change in mucositis score was associated with US$25,405 in additional hospital charges.[4]

## Current therapy options

Despite its severity and tenure, there are few approved treatment options for mucositis. In the United States, palifermin is the only approved intervention and it is solely indicated for patients with hematological malignancies receiving conditioning regimens in preparation for HSCT. Current evidence-based treatment approaches are delineated in the clinical practice guidelines produced by Multinational Association of Supportive Care in Cancer (MASCC) and published in 2007.[5] The panel's recommendations include strategies aimed at reducing the risk of oral mucositis by the practice of basic oral care, aggressive pain management for oral mucositis using morphine, and use of radiation techniques that minimize mucosal injury. Oral cryotherapy prior to administration of specific forms of chemotherapy was endorsed. Benzydamine HCl (not available in the United States) was recommended for patients undergoing radiation therapy for cancers of the head and neck. Palifermin, 60 μg/kg for three days prior to conditioning treatment and for three days post-transplantation was recommended for patients receiving high-dose chemotherapy with total body irradiation in preparation for autologous HSCT.

Although not included in the MASCC guidelines, the use of 'magic mouthwashes' for the treatment of oral mucositis is common.[6] 'Magic mouthwashes' encompass a range of palliative solutions that are locally formulated and largely ineffective.[7] While there is no uniformity in their composition, typically they include a mucoadherent vehicle such as milk of magnesia or Maalox® and a topical anesthetic such as lidocaine or Benadryl®. In addition, some include antifungal agents, steroids, and antibiotics. Typically the ingredients are based on institutional folklore as data supporting the efficacy of these solutions or their superiority over saline or bicarbonate rinses are lacking.

Another palliative alternative for patients with mucositis are those that fall into the device category. Barrier agents such a GelClair® and Mucotrol® are self-applied by patients in an attempt to cover ulcerated mucosa and reduce symptoms. Alternatively, a modified saline solution developed for remineralizing teeth in patients with xerostomia (Caphosol®) has also received approval as a device for mucositis. Studies supporting the use of these agents are sparse.

Relative to palifermin, two similar molecules, both in the fibroblast growth factor (FGF) super class, have been tested clinically: KGF-2 and FGF-20. In a phase I/II randomized, double-blind, placebo-controlled, multi-institutional study, Repifermin (KGF-2) significantly reduced the incidence of ulcerative mucositis in patients receiving mucotoxic chemotherapy as part of a conditioning regimen prior to autologous HSCT.[8] The study was sponsored by Human Genome Sciences, which has since ceased development of Rapifermin.

In 2005, CuraGen reported that subjects who received a single 0.03 mg/kg dose of velafermin (FGF-20) a reduced incidence of severe oral mucositis compared to those receiving placebo. The study, performed in patients receiving high-dose chemotherapy with or without total body irradiation

in preparation for autologous HSCT, failed to meet its primary endpoint as evaluated by predefined dose trend analysis. CuraGen did not continue development of the molecule.

## Unmet need

Oral mucositis is a clinically significant, burdensome toxicity of both head and neck radiation treatment and systemic chemotherapy. Currently an approved, effective intervention is available for only 4% of the at-risk population.

## Clinical studies with palifermin

Palifermin has been tested in randomized, double-blind, multi-institutional studies as an intervention for oral mucositis in three clinical settings: 1. conditioning regimens associated with autologous and allogeneic HSCT in patients with diagnosed hematologic malignancies; 2. cycled chemotherapy for the treatment of solid tumors (colorectal cancers); and 3. Radiation therapy with concomitant chemotherapy for the treatment of cancers of the head and neck.

### HSCT

The most supportive study for palifermin's efficacy as an intervention among patients receiving mucotoxic conditioning regimens prior to HSCT is provided by Spielberger and colleagues.[9] In this multicenter, double-blind, randomized, placebo-controlled trial of 212 autologous transplant recipients, palifermin was noted to: 1. reduce the incidence of severe (WHO grades 3, 4) mucositis from 98% in placebo-treated subjects to 63% in those receiving six doses (60 μg/kg, three doses prior to the start of conditioning and three doses following transplant) of palifermin ($p < 0.001$); 2. reduce the median duration of WHO grades 3, 4 mucositis from nine days to three days ($p < 0.001$); 3. reduce the incidence of WHO grade 4 mucositis from 62% to 20% ($p < 0.001$); and 4. significantly reduce patient reported mouth pain, opiod use, and use of total parenteral nutrition.

Two studies compared palifermin efficacy to retrospective controls. In a multicenter study Nasilowska-Adamska and colleagues[10] assessed the efficacy of palifermin in preventing oral mucositis in 53 patients who received conditioning regimens prior to either autologous or allogeneic HSCT. The response to palifermin was compared to a similarly sized, retrospective population matched for age, gender, diagnosis, disease state, and HSCT type. Unlike the Spielberger trial, subjects were being treated for both malignant and nonmalignant disease. Patients who received allogeneic HSCT received prophylaxis for graft-versus-host disease that included methotrexate. Palifermin was administered in the same dose and schedule as described by Spielberger.[9] The investigators reported that the incidence of WHO grades 1–4 was 58% in the palifermin-treated population compared to 94% in the retrospective controls ($p < 0.001$). The mean duration of all grades of mucositis was four days in the palifermin group versus nine days in the control group ($p < 0.001$). The population treated with palifermin used less analgesics, including opiods, and total parenteral nutrition (both $p < 0.001$).

In a second, multi-institutional unblinded trial in which palifermin was compared to retrospective controls, Langner and colleagues[11] reported their findings in 30 patients undergoing allogeneic HSCT for treatment of leukemia. Palifermin was administered using the same dosing regimen as described by Spielberger.[9] The majority of subjects received a highly mucotoxic conditioning regimen consisting of cytoxan and total body irradiation (TBI). Consistent with the earlier reports, the incidence of ulcerative mucositis (WHO grades 2–4) was less in palifermin-treated patients (60%), compared to the retrospective control group (86%; $p < 0.04$). While palifermin appeared to confer an advantage in reducing the incidence of more severe (WHO grades 3, 4) mucositis, the difference observed (controls 53%, palifermin 37%) was not significant ($p = 0.19$). In contrast, the mean duration of mucositis was significantly less when the two populations were compared (controls 12 days, palifermin six days, $p < 0.003$). Both opioid and TPN use were significantly less in palifermin-treated subjects.

The results of three single center studies have also been reported. Horsley and colleagues[12] reported that palifermin administered using the Spielberger-reported regimen to 32 patients undergoing HSCT was beneficial against mucositis compared to a 27 subject retrospective population. In contrast to the daily mucositis assessment performed in other trials, Horsley's group evaluated mucositis at a single time point (day 8) where they found that the incidence of severe mucositis (13%) was less than noted in the historical controls (48%; $p = 0.003$). They also noted that palifermin favorably affected swallowing problems, nutrition impact symptoms, and hospital length of stay.

Also using a historical control, Rzepecki and colleagues[13] found that patients receiving conditioning chemotherapy regimens prior to both autologous ($n = 11$) or allogeneic ($n = 9$) HSCT as treatment for hematologic malignancies benefited from palifermin treatment. They did not observe a single case of ulcerative mucositis, whereas the condition was noted in 50% of a retrospective control population had severe mucositis, typically lasting between 10 and 12 days. The palifermin cohort required fewer analgesics and days of antibiotics.

In a report of the first five HSCT patients to receive palifermin at the Royal Adelaide Hospital, Keefe and colleagues[14] found severe (WHO grade 4) mucositis in two subjects and WHO grade 2 in the remaining three. Duration of severe mucositis ranged from six days in one subject to 12 days in the other.

## Cycled chemotherapy

Palifermin has been studied in multicenter, double blind, placebo-controlled, randomized trials in patients receiving multicycle chemotherapy for the treatment of colorectal cancer. Using a randomized, placebo-controlled, dose-escalating study design, Meropol and colleagues conducted a multicenter trial to evaluate the efficacy of palifermin on attenuating ulcerative mucositis in 81 patients receiving fluorouracil (FU) and leucovorin for the treatment of measurable metastatic colon or rectal adenocarcinoma.[15] Subjects in the palifermin arm received three daily doses of the drug at one of six doses (range 1 μg/kg to 80 μg/kg) three days before the infusion of FU. The authors reported that the incidence of ulcerative mucositis was reduced from 67% among those being treated with placebo to 43% (not significant [NS]) in patients receiving any dose of palifermin. This trend was greatest for subjects receiving doses of palifermin >10 μg/kg. Although not significant, patient-reported outcomes also tracked in favor of palifermin.

In a subsequent phase II study, Rosen and colleagues[16] reported the effect of palifermin on the incidence of oral mucositis in a prospective, randomized, double-blind, placebo-controlled trial of 64 subjects. In this multicenter trial, 36 subjects were randomized to receive placebo. The remainder were treated with 40 μg/kg of palifermin for three consecutive days prior to infusion of FU and leucovorin. Patients were studied for two consecutive chemotherapy cycles. The authors reported that palifermin was superior to placebo in reducing the incidence of ulcerative mucositis (WHO grade ≥2) for both cycle 1 (palifermin 29% vs placebo 61%) and cycle 2 (palifermin 11% vs 47% placebo). In addition, patients who were treated with palifermin in cycle 1 were less likely to require chemotherapy dose reductions in cycle 2 (31% placebo vs 14% palifermin). Patient reported mouth and throat soreness was also reduced by the administration of palifermin.

Early results of a multicenter, randomized, double-blind, placebo-controlled trial in which palifermin was studied for its ability to prevent mucositis in sarcoma patients receiving doxorubicin-based chemotherapy were favorable.[17] Forty-eight sarcoma patients received placebo or palifermin 180 μg/kg as a single dose three days prior to chemotherapy in blinded fashion, or once a patient developed grade 3 mucositis, for up to six cycles of treatment. None of the subjects who received open-label palifermin (n = 7) developed WHO grade mucositis ≥3. The study is still being completed.

In an observational study of ten subjects treated at a single site with high-dose methotrexate[18] palifermin at a dose of 60 μg/kg administered for three days before and after (total six doses) methotrexate infusion reduced the maximum grade of oral mucositis in 10 patients who had previously experienced WHO grade ≥3. Opioid use was also reduced.

Finally, a case report in which a patient undergoing polychemotherapy for the treatment of a high grade B cell lymphoma describes the efficacy of palifermin (60 μg/kg given three days before and three days after chemotherapy) in preventing mucositis in a female patient who was hospitalized for mucositis during prior chemotherapy cycles.[19]

## Head and neck cancer

Mucositis is common and severe in patients receiving chemoradiation for the treatment of cancers of the mouth, oropharynx, larynx, and hypopharynx. In a multicenter, double-blind, randomized, placebo-controlled study Brizel and colleagues[20] evaluated the efficacy of palifermin in modulating mucositis in 67 patients compared to a control cohort of 32 subjects. Patients in the active group received ten weekly doses of palifermin 60 μg/kg administered starting on the Friday before the start of seven weeks of radiation therapy and continuing for two weeks after its completion. Subjects who received palifermin had a shorter duration of ulcerative mucositis (WHO grade ≥2) than did placebo-treated patients (6.5 weeks vs 8.1 weeks; NS). Palifermin appeared to be more effective in patients being treated with hyperfractionated (1.25 Gy twice daily) radiation than those who received standard (2 Gy once day) therapy.

Results of a multicenter, randomized, placebo-controlled, double-blind trial of palifermin in patients with locally advanced head and neck cancer were reported by Le and colleagues.[21] In this multinational study, half of the 188 enrolled subjects received palifermin (180 μg/kg) in weekly doses throughout their treatment with conventional courses of chemoradiation (radiation 2 Gy/day). The remaining subjects were treated with placebo. Palifermin favorably affected the incidence of severe mucositis (active 54% vs placebo 69%; p = 0.041), median duration of severe mucositis (active 5 days vs placebo 26 days) and time to onset of severe mucositis (active 47 days vs 35 days for placebo).

Henke and colleagues[22] reported the results of a multinational, multicenter, randomized, double-blind, placebo-controlled phase III study in which the efficacy of

palifermin was studied in 186 subjects also receiving a standard chemoradiation (2 Gy per day) dosing regimen. Active subjects were given 120 μg/kg of palifermin three days before the start of chemoradiation and then weekly throughout treatment. The incidence of severe mucositis was reduced in patients treated with palifermin (51%) compared to controls (67%; p = 0.027). Palifermin was also superior to placebo when median duration of severe oral mucositis (4.5 days vs 22 days) and time to onset were compared.

## Economic evidence

Using data obtained from a phase III trial of palifermin in a 212 subject HSCT cohort (see Spielberger and colleagues[9]), Elting and colleagues applied estimated costs of hospital stay from the National Inpatient Survey.[23] The cost estimates, based on charges using Medicare's state-specific cost-to-charge ratios were applied to study outcomes measures of incidence of febrile neutropenia, bacteremia/fungemia, pneumonia, and use of total parenteral nutrition. The mean cost of a hospital day in the HSCT population ranged from US$2,834 in the absence of adverse outcomes to US$4,663 when all of the above outcomes were present. Since administration of palifermin lowered the incidence of adverse outcomes, the savings achieved offset its price. An insignificant mean savings of US$3,595 per patient was associated with palifermin use.

## Patient group/population

Data support the use of palifermin in patients with hematologic malignancies who plan to receive mucotoxic conditioning regimens in preparation for HSCT.

Data supporting for the use of palifermin in the prevention of oral mucositis among patients being treated for carcinomas (colorectal or head and neck) is accumulating. Since this population constitutes the largest cohort of the mucositis at-risk population, the potential beneficial impact of an effective agent for mucosal protection is significant.

Assuming proof of efficacy, two barriers might impede the adoption of palifermin in this group: 1. palifermin is relatively expensive and cost-benefit will have to be demonstrated, especially in nonhead and neck cancer patients for whom the risk of significant mucositis is unpredictable and hovers around 20%–30% for the first cycle of chemotherapy; and 2. since epithelial tumors have receptors for KGF, some clinicians have voiced concern that palifermin has the potential to stimulate primary or secondary tumor growth. While there are no data to support this hypothesis, and xenograft models have demonstrated that palifermin neither stimulates tumor growth nor confers tumor protection from chemotherapy,[24] it is imperative that palifermin's inertia relative to tumor behavior be confirmed if the agent is to be widely accepted by the clinical community.

**Table 1** Evidence base included in the review

| Category | Number of records | |
|---|---|---|
| | Full papers | Abstracts |
| **Initial search** | | |
| Records excluded | 88 | 1 |
| Records included | 11 | 3 |
| Additional studies identified | 0 | 0 |
| Level 1 clinical evidence | 0 | 0 |
| Level 2 clinical evidence | 4 | 3 |
| Level ≥ 3 clinical evidence | 5 | 0 |
| Trials other than RCT | 1 | 0 |
| Case reports | 1 | 0 |
| Economic evidence | 1 | 0 |

**Notes:** For definitions of levels of evidence see the *Core Evidence* website (http://www.dovepress.com/core-evidence-journal).
**Abbreviation:** RCT, randomized controlled trial.

## Dosage, administration, and formulations

Palifermin (Kepivance®, Amgen/Biovitrum) is the 140 amino acid protein, human recombinant keratinocyte growth factor-1 (KGF-1), a member of the FGF super family. It is manufactured in *Escherichia coli* and supplied as a white, preservative-free, lyophilized powder that is reconstituted with sterile water for intravenous infusion. Kepivance® is dispensed in single-use vials containing 6.25 mg of palifermin, 50 mg of mannitol, 25 mg of sucrose, 1.94 mg of L-histidine, and 0.13 mg of polysorbate 20 (0.01%).

The following dosing information is quoted directly from the manufacturer's instructions for use:

The recommended dosage of Kepivance® is 60 mcg/kg/day, administered as an IV bolus injection for three consecutive days before and three consecutive days after myelotoxic therapy for a total of six doses.

### Pre-myelotoxic therapy

The first three doses should be administered prior to myelotoxic therapy, with the third dose 24 to 48 hours before myelotoxic therapy.

### Post-myelotoxic therapy

The last three doses should be administered post-myelotoxic therapy; the first of these doses should be administered after, but on the same day of hematopoietic stem cell infusion and at least four days after the most recent administration

of Kepivance®. No dose adjustment is recommended for patients with renal impairment. Kepivance is only approved for use in patients with hematologic malignancies planned to receive conditioning regimens in preparation for HSCT.

## Clinical value

Oral mucositis takes a significant toll on patients. Asked which toxicity of chemotherapy was most significant, patients who had received myeloablative chemotherapy or those receiving head and neck radiation placed mucositis at the top of their list. The lack of an effective agent to prevent and treat the condition has frustrated clinicians since the advent of cytotoxic cancer therapy. Palifermin is the first, mechanistically-based, approved intervention. Its efficacy in the HSCT population is proven. However, given the limited approved application of palifermin, its overall value has yet to be determined.

## Disclosure

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