CASE STUDY

Palifermin Use for the Prevention of Chemotherapy-Induced Oral Mucositis in Anal Cancer: A Case Report

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Background: Mucositis is a significant adverse effect of chemotherapy that often leads to treatment delays or to dose reductions. Palifermin is a human keratinocyte growth factor that is indicated to decrease the incidence and the duration of severe oral mucositis in patients with hematologic malignancies who are receiving myelotoxic therapy requiring hematopoietic stem-cell support. Limited data are available concerning the efficacy and the safety of palifermin in the setting of solid tumors.

Objectives: To describe the use of palifermin outside of its US Food and Drug Administration-approved indication in a 70-year-old patient with stage IIIC squamous-cell anal carcinoma for the secondary prevention of oral mucositis when using fluorouracil plus mitomycin concurrent with radiation therapy.

Discussion: This patient was treated according to the Nigro protocol, and he experienced severe mucositis associated with his first 4 days of treatment (World Health Organization grade 3) with significant pain for more than 2 weeks. On day 32, a single dose of palifermin 180 mcg was administered as an intravenous bolus. The patient was able to receive full-dose chemotherapy and radiation and did not experience adverse effects related to taking palifermin. Mucositis was minimal, with no pain reported by the patient and only 2 small superficial ulcers noted on physical examination.

Conclusion: To our knowledge, there are no other case reports of the use of palifermin to prevent oral mucositis in a patient receiving high-dose fluorouracil plus mitomycin concurrent with radiation therapy. Although our patient experienced great benefit from treatment with no adverse effects, the use of palifermin in nonhematologic malignancies remains controversial because of the potential concern of tumor growth stimulation and of interference with clinical outcomes.
Table 1  WHO Grading Scale for Assessment of Oral Mucositis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Soreness ± erythema, no ulceration</td>
</tr>
<tr>
<td>2</td>
<td>Erythema, ulcers; patients can swallow solid diet</td>
</tr>
<tr>
<td>3</td>
<td>Ulcers, extensive erythema; patients cannot swallow solid diet</td>
</tr>
<tr>
<td>4</td>
<td>Oral mucositis to the extent that alimentation is not possible</td>
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Palifermin is indicated to decrease the incidence and the duration of severe oral mucositis in patients with hematologic malignancies who are receiving myelotoxic therapy that requires hematopoietic stem-cell support. Palifermin’s mechanism of action is multifactorial. Palifermin increases the thickness of mucosal epithelium through its mitogenic effect, upregulates gene encoding for scavenging enzymes, and stimulates interleukin-13, which reduces tumor necrosis factor. In addition, palifermin exerts antiapoptotic effects and reduces angiogenesis.

The recommended dose of palifermin is 60 mcg/kg administered as an IV bolus daily for 3 days before conditioning treatment and for 3 days after myelotoxic therapy, thereby totaling 6 doses. The efficacy of palifermin has not been established in patients with nonhematologic malignancies.

The following case report describes the off-label use of palifermin to prevent oral mucositis in a patient receiving fluorouracil, mitomycin, and radiation for anal cancer.

Case Report
A 70-year-old man was diagnosed with anal cancer after a biopsy revealed invasive, moderately differentiated stage IIIc squamous-cell carcinoma. A positron emission tomography scan showed positive axial lesion and bilateral inguinal lymph nodes. The patient’s medical history was significant for obstructed sleep apnea, osteoarthritis, and hyperlipidemia. His social history included smoking of 60 pack-years and consumption of approximately 15 oz to 18 oz of alcohol weekly (10-12 mixed drinks weekly). His home medications included fluticasone 50-mcg nasal spray at bedtime, atorvastatin 10 mg daily at bedtime, diazepam 10 mg daily at bedtime, hydrochlorothiazide 12.5 mg daily, transdermal testosterone daily, vitamin E 100 U daily, and oxycodone plus acetyaminophen 10/650 mg every 6 hours as needed for pain.

Three weeks after his diagnosis, the patient was initiated on concurrent chemoradiation according to the Nigro regimen. The regimen consisted of 5-FU 1000 mg/m² daily (actual dose, 2100 mg over 24 hours) continuous IV infusion on days 1 to 4 and on days 29 to 32, and mitomycin 10 mg/m² (actual dose, 21 mg) as an IV bolus on days 1 and 29, concurrent with radiation therapy of 1.8 Gy daily, 5 days weekly for 5 weeks (total, 45 Gy). Before the first treatment, the review of systems and the patient’s physical examination were normal. His only complaint was some perianal discomfort and infrequent bleeding. The patient was otherwise healthy with an Eastern Cooperative Oncology Group Performance Status grade of 0.

On day 6, the patient was seen by the oncologist and...
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was found to have developed WHO grade 3 mucositis; oral mucosa was noted to be red with ulcer lesions and fissures at the corners of the lips. The patient described the pain as a 10 (on a scale of 0-10), with a burning, constant pain and the inability to swallow solid food, which started on day 3. The patient was still able to swallow liquids and medications. Pain management was initiated with oxycodone plus acetaminophen 10/325 mg every 4 hours as needed for pain, and fentanyl 25-mcg transdermal patch applied every 72 hours. Oral rinses every 4 hours with 5 mL to 10 mL of magic mouthwash (antacid, 30 mL; viscous lidocaine 2%, 50 mL; nystatin oral suspension 100,000 U/mL, 30 mL) and saline solution were started as well.

On day 10, the patient developed grade 3 neutropenia, and his laboratory values showed a white blood cell count of 1.1 K/µL and an absolute neutrophil count of 0.5 K/µL. The patient reported a pain level of 8 (scale, 0-10) despite taking pain medications as prescribed. The oral cavity was described as having moist oral mucosa, erythema of the tongue with small visible ulcers, and generalized redness. The decision was made to hold radiation from day 10 and to restart it on day 15 because of mucositis and neutropenia, and to start the patient on filgrastim 480 mcg daily subcutaneously for 3 days. The patient was instructed to continue using oral rinses (ie, magic mouthwash, baking soda, and salt solution).

On day 14, a physical examination revealed partial recovery of mucous membranes, although the patient still verbalized a pain level in the mouth of 8 and trouble swallowing. On day 17, a physical examination revealed moist oral mucosa without lesions, and the pain was rated as 4 on a scale of 0 to 10. On day 23, a physical examination revealed moist oral mucosa with erythema with no ulcer, and the patient rated his pain level as 0.

When the patient experienced 13 days of mucositis after chemotherapy treatment days 1 to 4, he refused further treatment out of fear of developing mucositis, despite several patient–provider discussions. The patient’s refusal led to a treatment delay. To address his concerns and to minimize subsequent toxicities, a number of options were evaluated, including a 25% dose reduction of the overall regimen and/or the omission of mitomycin from the regimen. However, these alternatives could possibly compromise the treatment’s effectiveness.

The option of a one-time dose of palifermin was presented to the physician and to the patient, although evidence of use in this setting was lacking. The decision was made to use palifermin off label as a single dose 3 days before the initiation of chemotherapy on day 35. The patient consented with this plan.

At 72 hours before receiving chemotherapy, the patient was administered palifermin 180 mcg/kg as an IV bolus in a single dose in the outpatient clinic, which the patient tolerated well. He was monitored in the infusion center for 2 hours postadministration and then discharged home. He also received filgrastim 480 mcg daily subcutaneously for 2 days on days 33 and 34 as prophylaxis for neutropenia. The patient was given education about the importance of good oral hygiene and about smoking cessation, but he never stopped smoking.

Chemotherapy was started on day 35. The patient received a full dose of fluorouracil 1000 mg/m² daily (actual dose, 2100 mg over 24 hours) in a continuous IV infusion on days 35 to 39 and mitomycin 10 mg/m² (actual dose, 21 mg) as an IV bolus on day 35. During a follow-up visit on day 39, the patient reported to be pain free, and a physical examination revealed moist oral mucosa without lesions.

In an interview with the patient, he stated that he did not experience any mucositis-related pain. On day 46, the patient came to the emergency department with a chief complaint of fever and chills and was admitted (temperature, 100°F; white blood cell count, 0.4 K/µL; absolute neutrophil count, 0.2 K/µL), where he received IV vancomycin and piperacillin plus tazobactam. On physical examination during this admission, the patient was noted as having pink mucous membranes, except for 2 small superficial ulcers.

The patient was discharged on day 49. Blood cultures that were taken on day 46 showed no growth at 5 days. During a follow-up visit on day 50, the physical examination revealed moist oral mucosa with 2 superficial oral ulcers and no mouth pain. The patient denied dysphagia and odynophagia. On day 66, he had no change of appetite, energy, or weight, and his oral mucosa was noted to be moist without lesions.

During a follow-up interview with the patient approximately 1 month after completion of the chemoradiation therapy, he stated that he experienced no mucositis-related pain. One year after completing treatment, he has no evidence of new soft tissue masses seen on computed tomography scan at 3 months, 6 months, 12 months, and 18 months posttreatment. The patient follows up regularly with the oncologist and with the colorectal surgeon.

**Discussion**

Patients may experience increased toxicities associated with their cancer treatments now that more intensive cancer therapies, including radiation, cytotoxic chemotherapy, and biologic-targeted therapies, are being used. One of the most significant of these toxicities is mucositis. Oral mucositis oftentimes is a dose-limiting toxicity. The development and evaluation of supportive agents that improve patients’ quality of life, as well as clinical
outcomes, are critical. By stimulating epithelial-cell proliferative activity, palifermin has a unique mechanism of action that is useful for the prevention of mucositis.

The use of palifermin in hematologic malignancies and stem-cell transplants has been established, but its efficacy in nonhematologic malignancies has yet to be conclusively determined. Several clinical trials have evaluated the use of palifermin in the prevention of mucositis in patients with solid tumors. A PubMed search for clinical trials that was limited to the past 15 years using the key words “palifermin,” “solid tumors,” and “mucositis” yielded several articles, as listed below and in Table 2.

Patients may experience increased toxicities associated with their cancer treatments now that more intensive cancer therapies, including radiation, cytotoxic chemotherapy, and biologic-targeted therapies, are being used. One of the most significant of these toxicities is mucositis.

A phase 1/2 randomized, double-blind, placebo-controlled study was conducted of patients with metastatic colorectal cancer who were receiving fluorouracil-based chemotherapy. Patients received leucovorin 20 mg/m² administered by IV injection, immediately followed by an IV bolus of fluorouracil 425 mg/m² once daily for 5 consecutive days. Patients received 2 chemotherapy cycles. The patients in the treatment arm received IV palifermin 40 mcg/kg daily for 3 consecutive days before chemotherapy.

The efficacy outcomes included incidence, duration, and severity of mucositis (WHO grades 2-4). Safety evaluations included adverse events, clinical laboratory values, and the development of antipalifermin antibodies. The incidence of WHO grade 2 or higher mucositis was significantly lower in the palifermin group versus in the group receiving placebo (29% vs 61%; \( P = .016 \)). The overall incidence of adverse events was comparable between the study groups. One patient in the study developed antipalifermin antibodies; titers were below the quantitation limit. Of note, fewer patients in the palifermin group required a chemotherapy dose reduction during cycle 2 than patients in the placebo group.

Vadhan-Raj and colleagues conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of palifermin when it is given as a single dose before each cycle of chemotherapy in 48 patients with sarcoma who had already experienced severe mucositis. Patients were given palifermin 180 mcg/kg or placebo intravenously as a single dose 3 days before chemotherapy with doxorubicin and ifosfamide in each cycle.

The primary end point was the incidence of moderate-to-severe mucositis (≥ grade 2). Patients in the palifermin group experienced a lower incidence of grade 2 or higher mucositis versus the placebo group (44% vs 88%, respectively; \( P < .001 \)). Common adverse events included patient-reported sensation of increased thickness of oral mucosa, altered taste, and a film coating in the mouth.

A phase 2 trial evaluated the efficacy of palifermin in patients receiving concurrent chemoradiotherapy for advanced head and neck squamous-cell carcinoma. Patients in the treatment arm were given 60 mcg/kg of palifermin once weekly for 10 doses.

The primary outcome of median duration of grade 2 or greater mucositis was shorter for palifermin than for placebo (6.5 and 8.1 weeks, respectively), but the difference was not significant (\( P = .157 \)). The proportion of patients who still had grade 2 mucositis at week 12 was 47% in the palifermin group and 42% in the placebo group. The authors noted that the palifermin dose may have been too low to show a significant difference, because the study was powered to detect a mean difference of 30%, based on results from a previous trial.

Le and colleagues conducted a multicenter, double-blind study of 188 patients receiving postoperative concurrent chemoradiotherapy (2.0 Gy daily, 5 days weekly, to 70 Gy) with cisplatin (100 mg/m² on days 1, 22, and 43) for locally advanced head and neck squamous-cell carcinoma. The patients in the study arm received palifermin 120 mcg/kg/3 days before treatment and then weekly for 7 weeks. The primary end point was the incidence of severe mucositis (WHO grades 3-4), in which significance was reached (54% vs 69%, respectively; \( P = .041 \)). Overall survival and progression-free survival were similar between the 2 arms after a median follow-up of almost 26 months.

Henke and colleagues studied the efficacy of palifermin in patients who were undergoing postoperative radiochemotherapy for head and neck cancer. This multicenter, double-blind, randomized trial enrolled 92 patients in the palifermin arm and 94 patients in the placebo arm. Patients received 60 Gy or 66 Gy of radiochemotherapy after complete (R0) or incomplete (R1) resection, respectively, at 2 Gy per fraction and 5 fractions weekly. Cisplatin 100 mg/m² was administered on days 1 and 22 (and on day 43 with R1 resection). Patients were randomly assigned to receive weekly palifermin 120 mcg/kg or placebo from 3 days before radiochemotherapy and continuing throughout radiochemotherapy.
## Table 2  
Recent Clinical Trials Using Palifermin for Solid Tumors and Mucositis

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Patients, N</th>
<th>Chemotherapy regimen</th>
<th>Palifermin dose</th>
<th>WHO criteria for mucositis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brizel, et al(^1)(^4)</td>
<td>Locally advanced head and neck</td>
<td>Placebo, 32 Palifermin, 69</td>
<td>Cisplatin 20 mg/m(^2) daily Fluorouracil 1000 mg/m(^2) daily CIVI for 4 days on weeks 1 and 5 Radiotherapy for 7 weeks</td>
<td>60 mcg/kg weekly for 10 weeks</td>
<td>≥Grade 2</td>
<td>Median duration, 6.5 weeks (palifermin) vs 8.1 weeks (placebo), (P = .157)</td>
</tr>
<tr>
<td>Vadhan-Raj, et al(^1)(^5)</td>
<td>Sarcoma</td>
<td>Placebo, 16 Palifermin, 32</td>
<td>Doxorubicin 90 mg/m(^2) CIVI over 72 hours and ifosfamide 10 g/m(^2) day for 4 days, or cisplatin 120 mg/m(^2) intra-arterially for osteosarcoma</td>
<td>180 mcg/kg as a single dose 3 days before chemotherapy cycle</td>
<td>≥Grade 2</td>
<td>Palifermin 44% vs placebo 88%, (P &lt; .001)</td>
</tr>
<tr>
<td>Rosen, et al(^1)(^6)</td>
<td>Metastatic colorectal</td>
<td>Placebo, 36 Palifermin, 28</td>
<td>Fluorouracil 425 mg/m(^2) day IV for 5 days Leucovorin 20 mg/m(^2) day for 5 days for 2 cycles</td>
<td>40 mcg/kg for 3 days before chemotherapy</td>
<td>≥Grade 2</td>
<td>Palifermin vs placebo, 29% vs 61%, respectively, (P = .016) for cycle 1; 11% vs 47%, (P = .003) for cycle 2</td>
</tr>
<tr>
<td>Le, et al(^1)(^9)</td>
<td>Locally advanced head and neck</td>
<td>Placebo, 94 Palifermin, 94</td>
<td>Cisplatin 100 mg/m(^2) on days 1, 22, and 43 of radiotherapy Fractionated radiotherapy (2.0 Gy, 5 days weekly to 70 Gy)</td>
<td>180 mcg/kg before starting chemotherapy and then once weekly for 7 weeks</td>
<td>Primary end point, grades 3-4</td>
<td>Palifermin 54% vs placebo 69%, (P = .041)</td>
</tr>
<tr>
<td>Henke, et al(^1)(^)(^0)</td>
<td>Locally advanced head and neck</td>
<td>Placebo, 94 Palifermin, 92</td>
<td>Cisplatin 100 mg/m(^2) on days 1 and 22 (day 43 for R1) Radiation 60 or 66 Gy after complete (R0) or incomplete resection (R1), respectively, at 2 Gy/fraction and 5 fractions weekly</td>
<td>120 mcg/kg weekly throughout radiochemotherapy starting 3 days earlier</td>
<td>Primary end point, grades 3-4</td>
<td>Palifermin 51% vs placebo 67%, (P = .027)</td>
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CIVI indicates continuous intravenous infusion; IV, intravenous; WHO, World Health Organization.
The primary end point was the incidence of severe oral mucositis (WHO grades 3-4). Patients in the palifermin group experienced severe oral mucositis at a significantly lower rate (51% vs 67%, respectively; P = .027) than in the placebo group. Adverse effects were similar between the 2 groups. Survival times for the palifermin and the placebo arms were nearly identical after a median follow-up of almost 33 months. The investigators cautioned against generalization of these results because of their small sample size.

A concern of using palifermin for multiple doses up to the day before chemotherapy for repeated cycles is that because mucosal tissue is rapidly proliferating, it may be more sensitive to chemotherapy-induced injury. In addition, if tumors were to express the KGF receptors, the administration of palifermin could theoretically lead to the stimulation of tumor growth.

The use of palifermin in the setting of solid tumors raises questions that are not applicable to the treatment of patients with hematologic malignancies, because epithelial cells express KGF receptors, whereas blood cells do not.17 A concern of using palifermin for multiple doses up to the day before chemotherapy for repeated cycles is that because mucosal tissue is rapidly proliferating, it may be more sensitive to chemotherapy-induced injury. In addition, if tumors were to express the KGF receptors, the administration of palifermin could theoretically lead to the stimulation of tumor growth and therefore interfere with disease outcomes, although in vitro and in vivo studies do not indicate a definitive role for KGF in tumor genesis.17 However, if the medication is given as a single dose, this issue may be avoided. Clinical studies that were conducted in patients with hematologic and solid tumor cancer did not show adverse clinical outcomes.14-16,18-20

Furthermore, in a phase 2 study of patients with head and neck squamous-cell carcinoma, mucosal cells in patients who were given a single dose of palifermin were shown to express cyclin E, a putative G1 marker, thereby suggesting that most of the mucosal cells were not actively dividing.15 In light of the experiences with erythropoietin-stimulating agents and their effect on tumor growth, it is important to assess the long-term safety of this KGF.

The patient described in this case report had several risk factors for the development of oral mucositis. Fluorouracil is known to be one of the agents with the highest risk of developing mucositis, and the addition of radiation to chemotherapy further increases this risk.12 Delaying radiation treatment, as was done during the first cycle, has been documented to lead to poorer outcomes.21 Additional patient-specific risk factors included his continued alcohol consumption and his tobacco use.

The patient received a dose of 180 mcg/kg of palifermin, corresponding to the dose that was used in the above-mentioned clinical trial by Vadhan-Raj and colleagues, which was available at the time.15 The study by Vadhan-Raj and colleagues also established the efficacy of palifermin as prophylaxis in patients who already experienced severe mucositis, as our patient did. Subsequent trials that were conducted in patients with head and neck cancer have been published with alternative dosing regimens with varying results. However, no data were available about the use of palifermin in a regimen of fluorouracil 1000 mg/m2 plus mitomycin 100 mg/m2 concurrent with radiation.

Our patient tolerated palifermin very well, with no complaints of adverse effects, which is consistent with experiences in the literature. The side effects tend to be mild for most patients, including altered taste and dry mouth.

To date, the patient described in this case report did not suffer any adverse clinical outcomes that could possibly be linked to his use of palifermin. However, we still have limited data on the use of palifermin in multiple doses for repeated cycles on clinical outcomes, such as survival rate and time to disease progression.

Our decision to use palifermin was made after other therapies (ie, oral rinses, cryotherapy) had failed to relieve the patient’s symptoms. Furthermore, our patient was refusing the continuation of chemoradiation, even though his disease was very curable. The positive experience from this case report cannot necessarily be extrapolated to patients with solid tumors, who are at a lower risk for developing mucositis.

**Conclusion**

Clinical trials of palifermin use in patients with solid tumors show promise, but there is little consistency across studies concerning dosing and primary end points. No clinical trials have evaluated the use of palifermin in high-dose fluorouracil therapy combined with radiation, such as the Nigro regimen. To our knowledge this is the first report of palifermin being used in a patient with anal cancer for the prevention of mucositis. Further research...
for the long-term safety and efficacy of palifermin in patients with nonhematologic malignancies is warranted. Palifermin may only be an option once other therapies are exhausted because of its possible effects on patient outcomes, especially in early-stage solid-tumor cancers. An extensive patient-specific risk-versus-benefit analysis needs to be conducted before using palifermin in this setting.

**Author Disclosure Statement**

Dr Brahim, Dr Kernan, Mr Ibrahim, Dr Nguyen, and Dr Ohana reported no conflicts of interest.

**References**


