A PROTECTIVE ROLE FOR KERATINOCYTE GROWTH FACTOR IN A MURINE MODEL OF CHEMOTHERAPY AND RADIOTHERAPY-INDUCED MUCOSITIS

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Purpose: To evaluate the activity of palifermin (rHuKGF) in a murine model of mucosal damage induced by a radiotherapy/chemotherapy (RT/CT) regimen mimicking treatment protocols used in head-and-neck cancer patients.

Methods and Materials: A model of mucosal damage induced by RT/CT was established by injecting female BDF1 mice with cisplatin (10 mg/kg) on Day 1; 5-fluorouracil (40 mg/kg/day) on Days 1–4, and irradiation (5 Gy/day) to the head and neck on Days 1–5. Palifermin was administered subcutaneously on Days 2 to 0 (5 mg/kg/day) and on Day 5 (5 mg/kg). Evaluations included body weight, organ weight (salivary glands and small intestine), epithelial thickness (esophagus and tongue), and cellular proliferation.

Results: Initiation of the radiochemotherapeutic regimen resulted in a reduction in body weight in control animals. Palifermin administration suppressed weight loss and resulted in increased organ weight (salivary glands and small intestine), epithelial thickness (esophagus and tongue), and cellular proliferation (tongue and salivary glands).

Conclusions: Administration of palifermin before RT/CT promotes cell proliferation and increases in epithelial thickness in the oral mucosa, salivary glands, and digestive tract. Palifermin administration before and after RT/CT mitigates weight loss and a trophic effect on the intestinal mucosa and salivary glands, suggesting that palifermin use should be investigated further in the RT/CT settings, in which intestinal mucositis and salivary gland dysfunction are predominant side effects of cytotoxic therapy. © 2006 Elsevier Inc.

INTRODUCTION

Chemotherapy and radiotherapy eliminate cancer cells, but their nonspecific targeting also destroys normal, healthy cells, particularly in epithelial tissues. Damage to the epithelium of the gastrointestinal tract results in a pathologic condition known as mucositis. This condition, induced by antineoplastic drugs and radiotherapy, is an important, dose-limiting, and costly side effect of anticancer therapy (1, 2). Patients with severe oral mucositis often develop ulcers that encompass the full thickness of the epithelium and penetrate into the submucosa causing extreme pain. In addition, the clinical sequelae of localized radiotherapy include xerostomia (dry mouth), loss of taste, and increased susceptibility to bacteremia and fungemia from loss of the barrier function of the epithelium, all of which have a negative impact on a patient’s quality of life (3). In the United States alone, approximately 400,000 cancer patients per year receiving chemotherapy develop oral complications and 40% of those develop some degree of oral mucositis, a condition in which destruction of the basal epithelium leads to atrophy, thinning, and ulceration of the mucosal epithelium (4). Additionally, cytotoxic regimens often cause myelosuppression, which further increases a patient’s risk of developing systemic infections (5–7).

Oral mucositis (OM) is particularly prevalent in patients receiving high-dose myeloablative chemotherapy/radiotherapy regimens that are used in the hematopoietic stem cell transplant setting. The incidence of OM is also high in head-and-neck cancer patients treated with fractionated radiation, with or without chemotherapy. Treatment of patients with head-and-neck cancer presents a particular challenge because radiation therapy frequently damages the normal epithelium of the oral cavity and salivary glands.

Acknowledgments—The authors thank Russ Cattley for review of the slides generated by in situ hybridization and immunohistochemical analyses and Elizabeth L. Pham for editorial assistance.

Received Dec 20, 2005, and in revised form April 26, 2006. Accepted for publication May 9, 2006.
Oropharyngeal mucositis has been characterized as the most debilitating side effect of radiation therapy in patients with head-and-neck cancer and can become a dose-limiting factor in this cancer population (3, 8). The most common interventions for OM include good oral hygiene, topical agents for pain, and parenteral nutrition (9–13). Agents under investigation include amifostine, sucrafate, glutamine, laser therapies, and granulocyte macrophage-colony stimulating factor (GM-CSF) mouthwash (14–20).

Keratinocyte growth factor (KGF) is a member of the fibroblast growth factor family (FGF-7) and binds to the tyrosine kinase KGF receptor (KGFRI/FGFR2IIIb), a splice variant of the FGFR2 (21). Activity of KGF is thereby limited to tissues that express KGFR. This receptor is expressed on the epithelial cells of multiple tissues, including the oral cavity, gastrointestinal tract, lung, prostate, skin epidermis, and hair follicles (22). KGF is secreted by mesenchymal cells and acts as a paracrine mediator for normal epithelial growth and differentiation (21). The well-documented activity of KGF in diverse epithelial tissues has led to extensive evaluation of the growth factor as a potential therapeutic agent for amelioration of cytotoxic therapy-induced mucositis (23–34).

Palifermin (ΔN23KGF), a recombinant form of human KGF, differs from the endogenous human KGF through the deletion of the first 23 N-terminal amino acids, which improves protein stability. Palifermin is approved in North America, Australia, and Europe to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy and hematopoietic stem cell transplantation. The safety and efficacy of palifermin in the nonhematologic setting have not been established. Thus the current study was designed to evaluate the activity of palifermin in a murine model subjected to a highly myeloablative radiotherapy/chemotherapy (RT/CT) regimen similar to the conditioning regimen used in the treatment of head-and-neck cancer patients.

MATERIALS AND METHODS

Recombinant human KGF production

Recombinant human KGF (palifermin) was produced in Escherichia coli, refolded, purified to homogeneity by conventional chromatography techniques, and tested to verify that it was endotoxin free. Palifermin was assayed in the BALB/MK keratinocyte cell line, as described previously (35). Palifermin was freshly prepared on each day of injection by reconstitution in phosphate-buffered saline to a final concentration of 0.5 mg/mL. Palifermin was administered subcutaneously at an injection volume of 0.2 mL per mouse. Dosage and route of administration were based on previous murine studies (29, 30).

Mice maintenance

Female BDF1 mice (Charles River Laboratories, Wilmington, MA) were used in all experiments. The protocols were performed at the Amgen Inc. Thousand Oaks site, which is accredited by the International Association for the Assessment and Accreditation of Laboratory Animal Care.

Radiotherapy and chemotherapy administration

Mice were injected with a single dose of intraperitoneal (IP) cisplatin (10 mg/kg; Bristol Myers Squibb, Princeton, NJ) on Day 1 at approximately 8:00 am. Cisplatin is used in the clinical setting as a radiosensitizer (36). To model multi-dose chemotherapy, mice were injected with 5-fluorouracil (5-FU) (40 mg/kg/day; Roche division Hoffmann-La Roche, Inc., Nutley, NJ) IP at approximately 9:00 AM on Days 1 to 4. This 5-FU regimen typically induces rapid loss of body weight followed by some recovery of body weight in surviving animals (29). To model clinical radiotherapy, mice were irradiated (5 Gy) at approximately 10:00 AM on Days 1 to 5 by exposure to a GammaCell 40 cesium source (Atomic Energy of Canada Limited, Kanata, ON, Canada). Mice were anesthetized with ketamine (Vetamine; Mallinckrodt Vet, Mundelein, IL) and xylazine (Rompu; Phoenix Scientific Inc, St. Joseph, MO) and placed in iron lead shields with only their heads exposed to the radiation to minimize whole-body exposure. The final concentration of anesthesia was ketamine 6.1 mg/mL and xylazine 0.4 mg/mL. A single dose of the drugs was administered intraorally in a volume of 0.5 to 0.55 mL per mouse (the mice weighed 20–25 g). The final dose for a mouse weighing 20 g was ketamine 150 mg/kg and xylazine 10 mg/kg. The mice were euthanized by CO₂ asphyxiation on Days 1, 6, and 8. Before initiation of the RT/CT regimen, mice received either palifermin (5 mg/kg/day for 3 days) or vehicle control (saline). Mice euthanized on Day 8 received a final injection of palifermin (5 mg/kg) post-RT/CT on Day 5. This pre-RT/CT and post-RT/CT administration of palifermin is referred to as palifermin therapy.

Analysis of body weight

Mice were weighed daily to determine changes in body weight over time. Mice were monitored closely for signs of morbidity for the duration of the experiments.

Target tissues and evaluated endpoints

The small intestine and salivary glands were weighed (wet weight) to establish the effect of palifermin on organ weight. Tongue, esophagus, and salivary glands were fixed, processed, and blocked in paraffin to facilitate morphometric analysis and evaluation by in situ hybridization and immunohistochemistry.

Tissues retrieved included the tongue (bisected longitudinally to capture dorsal and ventral surfaces), esophagus, small intestine, and salivary glands (submandibular and sublingual). Cell proliferation in the tongue, esophagus, small intestine, and salivary glands was examined through Ki67 (Novo Castra Laboratories Ltd., Newcastle-upon-Tyne, UK) staining or bromodeoxyuridine (BrdU) (Aldrich Chem. Co., Milwaukee, WI) incorporation. For the BrdU labeling, the mice were injected with BrdU (50 mg/kg) 1 h before sacrifice for tissue harvesting.

Epithelial thickness

Epithelial thickness (μm) was measured for tongue (dorsal and ventral surfaces) and esophagus. Morphometry of epithelial thickness was performed on hematoxylin and eosin-stained tissue sections using the MetaMorph image analyzer (Universal Imaging Corporation, Downingtown, PA). The full thickness of the nonkeratinized layer from the basement membrane of the basal layer to the interface with the keratinized nonnucleated layer of the dorsal and ventral surfaces of the tongue was divided into 21 to 24 equally spaced positions along the length of the surface in each of these regions (three to six fields per mouse and four measurements
per field). The positions were determined using a fixed grid overlay on the image. The esophageal epithelium was measured similarly with a total of 36 radial measurements (6 fields per mouse and 6 measurements per field). All tissue measurements were conducted in a blinded fashion. These measures were used to calculate group means ± standard error of the mean (SEM), n = 4 mice per group.

Immunohistochemical detection of Ki67 and BrdU

Tissue sections were evaluated for Ki67 expression as this is a well-established marker of cellular proliferation (37–39). Deparaffinized sections were pretreated with Antigen Retrieval Citra buffer (BioGenex, San Ramon, CA) and incubated with CAS BLOCK (Zymed Laboratories, San Francisco, CA). Next, sections were incubated with a rabbit polyclonal Ki67 antibody (Novo Castra Laboratories Ltd., Newcastle-upon-Tyne, UK) at a 1:800 dilution, followed by application of a biotinylated goat anti-rabbit secondary antibody (Vector Laboratories, Burlingame, CA). Tissue sections were quenched using a 3% solution of hydrogen peroxide and then incubated with an avidin-biotin complex (Vector Laboratories). Visualization of the reaction complex was achieved using a chromogen solution of 3, 3′-diaminobenzidine tetrahydrochloride (Dako Corporation, Carpinteria, CA) in the presence of a hematoxylin counterstain. The area of Ki67 immunoreactivity on each tongue and salivary gland tissue section was measured using the MetaMorph image analyzer (Universal Imaging Corporation, Downingtown, PA). Each group contained four mice. For each mouse, the area of immunoreactivity per μm length of basal lamina was measured and used to calculate a group mean (±SE). Alternatively, the Ki67 immunoreactive cells within each tissue section were counted and the percentage of Ki67-positive cells per microscopic field was determined. This percentage was used to calculate a group mean (±SE). Routine hematoxylin and eosin staining was also performed to verify morphologic integrity.

For BrdU staining, 5-μm tissue sections were deparaffinized, digested with 0.1% protease for 1 min, rinsed, and exposed to 2N HCl for 1 h to unravel the DNA. Tissues were incubated with a rat anti-BrdU monoclonal antibody (Accurate Chemical & Scientific Corporation, Westbury, NY) for 1 h, followed by a biotinylated rabbit anti-rat polyclonal antibody (Vector Laboratories) for 30 min, and a peroxidase-labeled avidin-biotin complex reagent (Vector Laboratories) for 30 min. Visualization was accomplished using 3, 3′-diaminobenzidine tetrahydrochloride as the chromogen.

Evaluation of KGFR expression by in situ hybridization

Formalin-fixed, paraffin-embedded tissue sections were evaluated for expression of the KGFR transcripts using in situ hybridization. The probe for the murine KGFR consisted of a 129 base pair fragment (GenBank accession number M63503, nucleotides 1270 to 1399) cloned into the pGEM4Z vector (Promega, Madison, WI). An anti-sense 33P-labeled RNA probe was synthesized with Sp6 RNA polymerase following linearization of the plasmid using a BamHI restriction enzyme. In situ hybridization was performed as described previously (40).

Statistical analyses

Data were statistically analyzed by ANOVA using StatView Software (SAS Institute Inc, Cary, NC). The Bonferroni/Dunn test was used to determine significance and calculate p values.

RESULTS

Expression of KGFR

We used in situ hybridization to evaluate the expression of KGFR in tissues of the upper digestive tract of normal mice treated with saline or palifermin. Expression of KGFR transcript was observed in the epithelial lining of the esophagus, dorsal and ventral tongue (Fig. 1). On the day after palifermin treatment, there was no observable difference in KGFR expression in the ventral and dorsal tongue isolated from palifermin-treated vs. vehicle-treated animals, but there was a slight increase in the level of staining in the esophagus of palifermin-treated mice. At 2 days after treatment with palifermin, the levels of transcripts in the tissues from the saline- and palifermin-treated mice were similar in the esophagus and ventral tongue, but there was a slight increase in KGFR expression in the dorsal tongue epithelium of the palifermin-treated mice. A weaker, more diffuse signal for KGFR was observed in the salivary gland tissue. Expression of KGFR was detected at similar levels in salivary gland tissues isolated from palifermin-treated and saline-treated animals (data not shown).

Epithelial cell proliferation after palifermin treatment

We used BrdU incorporation to analyze epithelial cell proliferation in the dorsal tongue, esophagus, and small intestine (jejunum) after treatment with palifermin. Twenty-four hours after treatment with palifermin, these tissues were collected and stained for BrdU incorporation into cells undergoing DNA synthesis (S-phase). In all tissues studied, treatment with palifermin resulted in a dramatic increase in the number of proliferating cells (Fig. 2, dorsal tongue and esophagus p < 0.0001; jejunum p < 0.01). The effect of palifermin on the epithelium of the submandibular and sublingual salivary glands was evaluated in another experiment where the mice were treated for 3 consecutive days with palifermin (5 mg/kg/day) before harvesting of the
tissues. The number of proliferating cells per microscopic field was assayed based on staining for the proliferation marker Ki67 staining (Fig. 3) and it was observed that palifermin treatment resulted in a significant increase in the number of proliferating epithelial cells in both the submandibular (\( p < 0.0001 \)) and sublingual salivary (\( p < 0.0009 \)) glands.

**Body weight changes after RT/CT**

Given the significant effects palifermin on the epithelial tissues of the gastrointestinal tract, we evaluated whether administration of palifermin (5 mg/kg daily injections on days −2 to 0 followed by a single post-RT/CT dose) could protect mice from RT/CT-associated side effects, specifically weight loss. Treatment with palifermin resulted in a significant improvement in reduction of weight loss in palifermin-treated mice compared with the vehicle-treated group (Fig. 4, \( p = 0.0128 \)). These data support a protective role for rHuKGF in diminishing the undesirable weight loss associated with RT/CT.

**Therapeutic effect of palifermin in RT/CT setting**

To further investigate if the possible protective effect of palifermin on body weight was due in part to a trophic action of palifermin on systemic target tissues, the small intestine and salivary glands were recovered from the mice and weighed before the initiation of RT/CT. Tissue weights from the mice treated with palifermin for 3 days (5 mg/kg/day on days −2 to 0) were compared with those from animals that received vehicle alone. As shown in Fig. 5, the 3-day course of palifermin treatment resulted in a significant increase in the mean wet weight of the small intestine (Day 1: small intestine \( p < 0.05 \)). In animals that received vehicle alone, initiation of RT/CT resulted in a significant decrease in wet weight for the small intestine (Days 6 and 8: small intestine \( p < 0.0001 \)). After initiation of the RT/CT regimen, the wet weight of the small intestine in the palifermin-treated was significantly higher than in the vehicle-treated control group (Days 6 and 8: \( p < 0.05 \)), indicating a protective effect of palifermin in preventing intestinal damage.
The impact of palifermin treatment on the wet weight of the salivary glands was assessed, as this tissue was shown to express the KGFR and to respond to palifermin in normal mice. Before initiation of the RT/CT regimen (Day 0), the 3-day palifermin pretreatment resulted in increased wet weight for the salivary glands compared with glands isolated from vehicle-treated animals, but this increase was not statistically significant (data not shown). In post-RT/CT treated animals (Day 8), the 3-day palifermin treatment significantly increased the tissue wet weight of the salivary glands compared with the vehicle-treated group (Day 1: dorsal and ventral tongue \( p < 0.0001 \); esophagus \( p < 0.05 \)). Initiation of the RT/CT regimen resulted in decreased epithelial thickness in both the tongue and esophagus in animals that received vehicle alone (Day 6: esophagus \( p = 0.0006 \)). In the RT/CT treated animals, administration of palifermin on days –2 to 0 followed by a single dose post-RT/CT resulted in a significant increase in epithelial thickness of the tongue and esophagus compared to saline-treated mice (dorsal and ventral tongue; \( p < 0.0001 \) on Days 6 and 8; esophagus; \( p < 0.05 \) on Day 6). These data indicate that palifermin treatment helped prevent mucositis as measured by the reduction in epithelial thickness in the tongue and esophagus that occurs as a result of the cytotoxic damage induced by the CT/RT regimen.

**DISCUSSION**

For patients with advanced head-and-neck cancer, new treatment modalities based on fractionated locoregional ra-

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Fig. 3. The effect of palifermin on the proliferative capacity (Ki67) of murine salivary glands. Groups of mice were euthanized on Day 0 before initiation of radiotherapy/chemotherapy. Salivary gland tissue was removed and immunostained for Ki67 as described. (a) The percentage of Ki67-positive cells in the submandibular and sublingual glands per microscopic field was determined and the mean value per group (±SE) (n = 4 mice) is presented: *\( p < 0.0001 \) compared with matched control; **\( p < 0.0009 \) compared with matched control. (b) Ki67 immunostaining of cross-sections of the submandibular and sublingual glands.

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As shown in Fig. 6, administration of palifermin to mice before the RT/CT regimen resulted in a significant increase in the thickness of the epithelium in the tongue (dorsal and ventral surfaces) and esophagus compared with the vehicle-treated group (Day 1: dorsal and ventral tongue \( p < 0.0001 \); esophagus \( p < 0.05 \)). As shown in Fig. 6, administration of palifermin to mice before the RT/CT regimen resulted in a significant increase in the thickness of the epithelium in the tongue (dorsal and ventral surfaces) and esophagus compared with the vehicle-treated group (Day 1: dorsal and ventral tongue \( p < 0.0001 \); esophagus \( p < 0.05 \)).
diation in combination with chemotherapy has led to improved tumor control rates (41–46). Such aggressive radiotherapy treatment regimens, in combination with chemotherapeutic agents such as 5-FU, methotrexate, and doxorubicin, often result in more frequent and severe acute oral toxicities that can significantly affect quality of life, compromise optimal therapeutic regimens due to dose reduction or modification, adversely affect local tumor control, and shorten patient survival (3, 43, 47, 48). Failure to deliver planned doses of chemotherapy on time, or use of low-dose chemotherapy, have similarly been associated with poorer outcomes in some malignant diseases (49, 50).

Current approaches to manage oral mucositis include systemic and topical approaches, including cytokines and other inflammation modifiers (interleukin-1, interleukin-11, and transforming growth factor-β3), amino acid supplements (L-glutamine), colony-stimulating factors, and laser therapy, with limited efficacy (4, 51). Treatment modalities ameliorating the deleterious side effects of current anticancer therapy regimens are essential to facilitate treatment intensification for patients with high-risk disease, to reduce treatment-related morbidity, and to improve the quality of life for patients undergoing RT/CT.

This study determined the effects of palifermin administration in a murine model of RT/CT-induced mucositis that mimics the cytotoxic regimen used in head-and-neck cancer patients. We used a combination of chemoradiotherapy because this dual modality has been reported to be more efficacious than radiotherapy alone in the treatment of patients with advanced head-and-neck cancer (42, 52). In a previous study of mice exposed to whole-body irradiation, palifermin reversed the inhibition of cellular proliferation and prevented atrophy of the small intestine, as observed in control mice treated with radiation only (40). We subjected mice to a combination of focal radiation and chemotherapy and explored the use of palifermin to prevent the mucotoxicities associated with the RT/CT regimen. We observed an increase in organ weight, epithelial thickness, and cellular proliferation in the salivary glands, tissues of the upper aerodigestive tract (esophagus and tongue), and lower digestive tract (jejunum). These effects correlated with a better weight control in the palifermin-treated mice as demonstrated by a smaller decrease in body weight compared with control mice treated with saline.

The observed palifermin effects were likely mediated through KGFR on epithelial cells. Evidence from the literature indicates that KGF binds only to a specific splice variant of the FGFR2 (FGFR2IIIb), which is primarily expressed in epithelial tissues (53). In situ hybridization for KGFR expression showed that transcripts of KGFR were readily detectable in the dorsal and ventral tongue, esophagus, and the salivary gland epithelia. No major difference was observed in the level of KGFR expression in tissues isolated from palifermin-treated vs. saline-treated animals, indicating that the transcript levels of KGFR were not downregulated after stimulation of the receptor. Cellular proliferation was increased significantly in the tongue, esophagus, and salivary gland tissues in palifermin-treated mice compared with vehicle control highlighting the responsiveness of both tissues to palifermin. Before initiation of the RT/CT regimen, treatment with palifermin for 3 days resulted in stimulation of the growth of tissues of the aerodigestive and gastrointestinal tracts as well as the salivary glands, manifested primarily as increases in wet weight and epithelial thickness. In animals exposed to the RT/CT

![Figure 5](image-url)

Fig. 5. The effect of palifermin on organ weight in mice treated with cisplatin, 5-fluorouracil (5-FU), and localized irradiation. The Day 1 time point corresponds to mice that were euthanized just before the initiation of radiotherapy/chemotherapy. The remaining mice were given cisplatin, 5-FU, and radiation and euthanized on Days 6 and 8. After euthanization, organs were excised and wet weights were determined. (a) Changes in small intestine weight in control and palifermin-treated mice administered cisplatin, 5-FU, and localized irradiation. The mean weight per group ± SE is reported: *p < 0.001; **p < 0.05 compared with control Day 1. (b) Changes in salivary gland weight in control and palifermin-treated mice administered cisplatin, 5-FU, and localized irradiation. The data presented correspond to animals euthanized on Day 8 (palifermin or control). After euthanization, salivary glands were excised and wet weights were determined. The mean weight per group ± SE was calculated and is presented: **p < 0.05 compared with matched control.
regimen, the 3-day treatment with palifermin resulted in protection from the cytotoxic effects of cisplatin, 5-FU, and radiation. The RT/CT regimen resulted in a decrease in epithelial thickness in the tongue and esophagus and wet weight of the small intestine and salivary glands, which were significantly ameliorated in the palifermin-treated mice. Palifermin administration to both normal and RT/CT-treated mice had major effects on the salivary glands. In normal mice, we observed a rapid increase in epithelial cell proliferation in the submandibular and sublingual salivary glands after 3 days of palifermin treatment. In mice receiving RT/CT, palifermin treatment for 3 days before cytotoxic therapy followed by a single dose after the end of RT/CT led to a significant increase in the wet weight of the salivary glands compared with control mice treated with saline.

Radiation therapy for malignant head-and-neck tumors is mainly responsible for the damage to the salivary glands, which are often included in the radiation field because of the proximity to the tumor mass (52). Xerostomia (i.e., dry mouth from the lack of saliva production) is the major symptom of this condition and there is no routine treatment for radiation-induced salivary dysfunction. In addition to oral mucositis, xerostomia has now been included as one of the endpoints in current clinical trials conducted to evaluate the therapeutic efficacy of palifermin in head-and-neck cancer patients receiving RT/CT regimens. Our data suggest that the palifermin activity on salivary glands might be of potential benefit for clinical use in patients to prevent inadvertent damage to the salivary glands from RT or CT cytotoxic regimens.

The present study provides evidence that administration of palifermin promotes cell proliferation and increases epithelial thickness in the oral mucosa, salivary glands, and digestive tract. Administration of palifermin before and after RT/CT mitigates weight loss and a trophic effect on the intestinal mucosa and salivary glands.
glands. These data suggest moving forward with investigating the use of palifermin to prevent the incidence of intestinal mucositis and xerostomia in cancer patients being treated with radiation and chemotherapy.

REFERENCES


