Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis

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Oral and intestinal mucositis are among the most significant dose-limiting toxic effects of intensive cancer treatment and are associated with adverse clinical and economic outcomes. Palifermin (Kepivance™), an N-truncated recombinant human keratinocyte growth factor-1, is the first agent to be approved for prevention of oral mucositis. Keratinocyte growth factor, a potent epithelial mitogen, appears to play a major role in the healing process. Palifermin has multiple biological activities that appear to protect the mucosal epithelium and promote its early regeneration after irradiation- and chemotherapy-induced injury. These include inhibition of epithelial cell apoptosis and DNA damage, up-regulation of detoxifying enzymes and down-regulation of pro-inflammatory cytokines, as well as enhanced migration, proliferation and differentiation of epithelial cells. Palifermin reduces the incidence, severity and duration of oral mucositis in patients with haematological malignancies undergoing myelotoxic conditioning therapy and haematopoietic stem-cell transplantation. Clinical sequelae, including febrile neutropenia and resource use (opioid analgesia and parenteral feeding), are concomitantly reduced. Other potential applications being explored include use in the solid tumour setting, reduction of intestinal mucositis and reduction of GVHD in allogenic transplantation. Thus, the development of palifermin and other potential new agents for preventing chemotherapy- and radiotherapy-induced mucositis represents an important breakthrough in oncological supportive care.

Key words: anti-neoplastic agents, adverse effects, growth factors, haematopoietic stem-cell transplantation, keratinocyte growth factor, mucositis, palifermin

introduction

The rapidly proliferating epithelia of the oral and gastrointestinal (GI) mucosa are extremely sensitive to damage induced by radiation and chemotherapy [1–4]. Mucosal barrier injury (MBI) can extend throughout the alimentary tract and its clinical manifestations, oral, oesophageal and intestinal mucositis, are among the most significant dose-limiting toxic effects of intensive cancer treatment.

Oral mucositis is characterised clinically by pain, erythema and the formation of deep, diffuse ulcers that are often covered by pseudomembranes. It is particularly common in patients undergoing myelotoxic conditioning regimens (high-dose chemotherapy with or without radiotherapy) before bone marrow transplantation (BMT) or haematopoietic stem-cell transplantation (HSCT), affecting up to 100% of patients [5–7]. Oral mucositis is rated as the most debilitating and troublesome adverse effect of cancer treatment by patients undergoing HSCT [8] or radiotherapy for head and neck cancer [9]. It can cause difficulty with speaking, swallowing and alimentation and significantly impair daily functioning and quality of life (QoL) [10, 11], and may necessitate opioid analgesia, a liquid diet, IV hydration and/or total parenteral nutrition (TPN).

GI mucositis, characterised by nausea, vomiting, abdominal pain and watery diarrhoea, sometimes with macroscopic blood loss, often accompanies oral mucositis in patients undergoing HSCT, but its severity may be masked by administration of antiemetics and/or opioids. Chemotherapy-induced GI MBI is most prominent in the small intestine but also affects the stomach and large intestine. Progression of intestinal mucositis can lead to colitis, obstruction, necrosis, fistula formation or perforation. Typhlitis (also called neutropenic enterocolitis), which usually involves the caecum, is the most serious form of MBI and has a high mortality rate [12]. It is possible that GI MBI may trigger acute graft-versus-host disease (GVHD) in the...
allogeneic transplantation setting. Indeed, it is suggested that the GI tract is not only a major target of GVHD but also critical to propagation of the ‘cytokine storm’ that characterises acute GVHD [13].

Mucositis increases the risk of sepsis [7, 14–16] and bleeding [14, 17], and in the multicycle chemotherapy setting can lead to delayed treatment cycles or reduced dosage, thereby potentially compromising local tumour control and survival [18, 19]. Mucositis has also been shown to increase healthcare resource use, prolong hospital stay and increase associated costs [10, 14, 17], as well as increasing mortality risk [14, 17, 20]. Indeed, recent data have shown that severe mucositis can have a profound negative impact on long-term survival in patients with lymphoid malignancies undergoing autologous stem-cell transplantation [20].

Until recently, standard management options for mucositis were essentially palliative and included such approaches as oral hygiene, protective coating agents, topical anaesthetics/analgescics and systemic analgesia. Indeed, evidence-based clinical guidelines from the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology concluded that evidence was insufficient to support the recommendation of many agents that are in use [21].

An increased understanding of the underlying pathobiology of mucositis has led to identification of a number of potential mechanistically based approaches that are now becoming available for clinical use. Palifermin (Kepivance™, Amgen), an N-truncated (ΔN23KGF) form of recombinant human keratinocyte growth factor (KGF)-1, recently became the first agent to be approved as an intervention for oral mucositis following an aggressive conditioning regimen requiring HSCT in patients with haematological malignancies [22]. KGF-1 [also designated as fibroblast growth factor (FGF)-7] is a 28-KDa heparin-binding member of the FGF family that is synthesised exclusively by mesenchymal cells, particularly fibroblasts [23].

KGF is a paracrine modulator of mesenchymal-epithelial communication that plays a key role in maintaining the barrier function of epithelial tissues and the healing process after injury [23].

This article reviews clinical and preclinical data on palifermin that are relevant to chemotherapy- and radiotherapy-induced mucositis and examines its biological activities in the light of current perspectives on the pathobiology of this condition.

pathobiology of MBI

MBI was previously thought to be solely an epithelium-mediated event resulting from direct damage by chemotherapy or radiotherapy to the basal epithelial cell layer, leading to loss of renewal capacity and subsequent clonogenic cell death, atrophy and ulceration. However, it has been demonstrated more recently that MBI is mediated largely by a series of complex and dynamic interactions involving the endothelium, extracellular matrix, a submucosal cellular infiltrate and connective tissue [24, 25].

A pathobiological model for oral mucositis has been proposed by Sonis [24], consisting of five phases: initiation, up-regulation, signal amplification, ulceration and, finally, healing (Figure 1).

This model is fundamentally likely to be applicable to GI mucositis, although it should be noted that there are anatomical, functional, immunological and microbiological differences between the stratified squamous epithelium of the mouth and oesophagus and the columnar epithelium of the gut. Moreover, the patterns of mucositis and healing vary according to the regimen given [7, 26].

stages of mucositis

initiation. DNA and non-DNA damage caused by chemotherapy or radiotherapy results in generation of reactive oxygen species (ROS). This activates a cascade of downstream events, affecting endothelial as well as epithelial targets [24, 27].

up-regulation. DNA and non-DNA damage and ROS production activate transcription factors, such as p53 and nuclear factor (NF)-κB. Chemo/radiotherapy also directly activates transcription factors. This results in over- and under-expression of a variety of genes that lead to production of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α. At the same time, anti-inflammatory cytokines from the epithelium and cells in the lamina propria are probably attenuated. These events initiate tissue injury and apoptosis. Radiation, chemotherapy and ROS also activate the pro-apoptotic ceramide and sphingomyelinase pathways. The resulting fibroblast destruction generates fibronectin, metalloproteinases and further apoptosis [24, 27].

The damage that results is a function of the renewal time for each epithelial type. Thus, intestinal epithelium damage occurs rapidly, often becoming apparent within 48 h of insult. In contrast, oral, oesophageal and rectal mucosae do not demonstrate breakdown for as long as a week following chemotherapy. The kinetics of radiotherapy-induced injury are a function not only of time but also of cumulative dose [2, 4, 28, 29].

signal amplification. A range of biologically active proteins accumulates and targets the submucosal tissue. Some of these proteins, particularly the pro-inflammatory cytokines, provide positive feedback loops that amplify the primary damage response. For instance, TNF-α activates the sphingomyelinase/ceramide, caspase, mitogen-activated protein kinase (MAPK), cyclooxygenase-2 (COX-2) and tyrosine kinase pathways, as well as the transcription pathway mediated by NF-κB, resulting in increased production of IL-1β, IL-6 and TNF-α [24, 27].

The role of COX-2 is unclear, but it may intensify and prolong mucositis via interaction with pro-apoptotic pathways and NF-κB [30].

ulceration. The breakdown of the mucosa results in lesions that may be exacerbated by local bacterial colonisation, as a barrage of cell-wall products penetrates the submucosa and activates infiltrating mononuclear cells to release additional pro-inflammatory cytokines [31]. A fibrinous exudate (pseudomembrane) may be evident on mouth ulcers. In the small intestine, the key features of MBI are loss of epithelial surface and altered permeability [32, 33], reflecting crypt and villus atrophy [34], with depletion of goblet cells and
down-regulation of protective trefoil proteins [35]. These events are accompanied by opening of the ‘tight junctions’ [34] between intestinal cells that maintain the integrity of the epithelial barrier and control the flow of solutes through extracellular spaces. TNF-α, interferon (IFN)-γ and IL-1 play key roles in the changes in functionality, permeability, brush border transport, glutamine utilisation and mucosal cell integrity that occur in intestinal MBI [36].

This is the stage at which the patient is at risk of complications. The loss of mucosal barrier function provides a portal of entry for resident microflora, which translocate from the intestinal lumen to the mesenteric lymph nodes, spleen and liver, potentially leading to bacteraemia and sepsis, particularly in neutropenic patients. Moreover, pro-inflammatory bacterial oligopeptides, including endotoxin [lipopolysaccharide (LPS)], penetrate into the systemic circulation [37] and increase intestinal permeability, either via direct effects [38] or by stimulating release of pro-inflammatory cytokines such as TNF-α [39, 40]. These events have been implicated in development of fever of unknown origin [41].

healing. Healing of the mucosa is initiated by a signal from the extracellular matrix. Epithelial cells migrate to cover denuded areas (restitution), then proliferate and differentiate to rebuild the mucosa. A number of cytokines, chemokines and growth factors are involved in epithelial restitution. Epidermal growth factor (EGF), transforming growth factor (TGF)-β, IL-1β and IFN-γ appear to promote this process by up-regulating TGF-β, which may stimulate expression of lamina β chain, fibronectin and collagen type IV [42]. Trefoil family factors, small proteins secreted by mucus-secreting cells of the intestinal mucosa, play an important role in healing, possibly by organising the protective mucin layer [43] and promoting cell differentiation [35]. They appear to act via mechanisms that are distinct from those of cytokines and growth factors and not dependent on TGF-β [42].

Endogenous KGF is up-regulated after injury by growth factors, such as platelet-derived growth factor BB and TGF-α [23], and appears to play a major role in the normal healing process [23, 44, 45]. It is a potent epithelial mitogen, stimulating the growth and development of epithelial cells in many different organs, including skin, intestine, bladder and lungs [23]. While oral mucositis generally resolves within 2–3 weeks, GI integrity and function do not recover for several more weeks, with malabsorption and decreased enzyme activity persisting after structural repair is complete [26]. Indeed, the oral mucosa does not return completely to its preinjury state and is now more susceptible to subsequent injury [24, 27].
**palifermin in mucositis**

**preclinical data**

Palifermin mimics the actions of endogenous KGF, binding specifically to a tyrosine kinase receptor fibroblast growth factor receptor (FGFR2b), which is uniquely expressed in epithelial cells in a variety of tissues, including epidermis; hair follicles; oral, GI and lung epithelium and urothelium [46] (Figure 2).

Animal studies have shown that it enhances the regenerative capacity of epithelial tissues. It prevents oral and intestinal MBI induced by chemotherapy and irradiation [47–54] and markedly reduces mortality associated with intestinal mucositis [49, 54]. The timing of palifermin administration is critical, as pre-exposure administration induces a number of cellular responses that appear to collectively reinforce the epithelial barrier and increase tolerance to subsequent chemo/radiotherapy.

The underlying mechanisms of action of palifermin in ameliorating mucositis are incompletely elucidated. Multiple biological actions have been reported, although some of these are on the basis of limited and/or in vitro data and require verification. They can be broadly divided into three categories: cytoprotective effects, modulation of cytokine profile and trophic/regenerative effects.

**cytoprotective effects.** Palifermin has a number of biological effects that together limit cellular damage:

- Up-regulation of detoxifying enzymes such as nonselenium glutathione peroxidase (peroxiredoxin VI) and glutathione-S-transferase that protect against ROS [47, 56]. This may be mediated via up-regulation of the transcription factor, NF-E2-related factor (Nrf) 2, which mediates the cellular response to stress via the antioxidant response element, and the related factor Nrf3 [57].
- Prevention of DNA strand breaks [58–60], possibly via activation/up-regulation of DNA polymerases, protein kinase C and/or tyrosine kinase [58, 59].
- Inhibition of epithelial cell apoptosis [61–64], possibly via modulation of apoptotic/antiapoptotic factors such as Bcl-2 [61], Bax, Bcl-x, p53 [65], Akt [64, 66] and p21-activated protein kinase 4 [67].

**modulation of cytokine profile.** Palifermin appears to alter the cytokine profile from a helper T-cell type (Th) 1 towards a Th2 balance:

- Down-regulation of the Th1 pro-inflammatory cytokines TNF-α [68, 69] and IFN-γ [69, 70].
- Up-regulation of the Th2 cytokines IL-4 [70, 71] and IL-13 [69–71].

**trophic/regenerative effects.** Palifermin induces trophic effects on the oral and intestinal mucosa, in healthy volunteers [72] and animals [48, 73, 74] and prevents atrophic changes in these tissues in animal models of chemo/radiotherapy-induced injury:

- Reduction of atrophy and ulcer formation and accelerated regrowth in the oral epithelium in animal models of irradiation- and chemotherapy-induced injury [48, 50–52].
- Prevention of villus atrophy and enhanced survival/proliferation of crypt cells and goblet cells in the intestine after chemo/therapy/irradiation [49, 75].
- Enhanced small intestine and/or colonic mucosal growth, repair and barrier function in animal models of malnutrition, TPN and intestinal inflammation [23, 56, 62, 63, 76].
- Enhanced migration, spreading, proliferation and differentiation of epithelial cells [48, 74, 77, 78], with an increase in stem cell numbers and number of stem cells in the S phase of the cell cycle [73] and enhanced epithelial cell tight junctions [79].

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**Figure 2.** Cellular mechanism of palifermin. TK, tyrosine kinase.
• Up-regulation of the protective intestinal trefoil proteins trefoil factor (TFF)2 and TFF3 [80] and goblet cell secretor [81],
• Inhibition of desquamation via increased cell–cell adhesion [23], mediated by increased numbers of desmosomes [48],
• An increased number and size of keratohyalin granules in the cells of the suprabasal layers [48],
• Stimulation of the EGF receptor [77], via increased TGF-α secretion [82, 83],
• Up-regulation of proteases that are active in tissue remodelling [23].

clinical efficacy
Palifermin has been evaluated for prevention of oral mucositis in the context of high-dose chemotherapy with or without radiotherapy before HSCT for haematological cancers and multicycle chemotherapy for solid tumours (Table 1).

Although most studies were phase I–II, all were placebo-controlled to allow differentiation of the effects of palifermin treatment from those of cancer therapy. Oral mucositis was evaluated using the World Health Organization (WHO) scales: grade 0 (none), grade 1 (oral soreness, erythema), grade 2 (oral erythema, ulcers, solid diet tolerated), grade 3 (oral ulcers, liquid diet only) or grade 4 (oral alimentation not possible).

Table 1. Palifermin: clinical studies in oral mucositis (all placebo controlled)*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Palifermin dosage</th>
<th>Cancer type (total no. of patients)</th>
<th>Radiotherapy regimen</th>
<th>Chemotherapy regimen</th>
<th>Effect on mucositis: palifermin versus placebo</th>
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<td>Incidence (% of patients) Duration (days)</td>
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<td>High-dose chemotherapy ± radiotherapy + HSCT</td>
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<td>Phase I–II</td>
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<tr>
<td>Durrant et al. 1999 [84]</td>
<td>5–80 μg/kg/day × 3 (pre) or 6 (pre/post)</td>
<td>Lymphoma (234)</td>
<td>–</td>
<td>BEAM</td>
<td>13% versus 51%b (WHO grade 2–4) Mean 0.8 versus 4.6b (WHO grade 2–4)</td>
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<tr>
<td>Spielberger et al. 2001 [85]</td>
<td>60 μg/kg/day × 3 (pre) or 6 (pre/post)</td>
<td>Haematological (129)</td>
<td>12 Gy TBI</td>
<td>ETO 60 mg/kg + CYC 75 or 100 mg/kg</td>
<td>Mean 5.0 (3 doses) or 4.0 (6 doses) versus 7.7 days (WHO grade 3–4; P &lt; 0.04 and &lt; 0.001)</td>
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<td>Phase III</td>
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<tr>
<td>Spielberger et al. 2004 [22]</td>
<td>60 μg/kg/day × 6 (pre/post)</td>
<td>Haematological (212)</td>
<td>12 Gy TBI</td>
<td>ETO 60 mg/kg + CYC 100 mg/kg</td>
<td>63% versus 98% (WHO grade 3–4; P &lt; 0.001) Median 6.0 versus 9.0 (WHO grade 3–4; P &lt; 0.001)</td>
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<td>Multicycle chemotherapy: solid tumours (Phase I–II)</td>
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<td>Clarke et al. 2001 [86]</td>
<td>40 μg/kg/day × 3 per cycle (pre)</td>
<td>Advanced colorectal (64)</td>
<td>–</td>
<td>5-FU 425 mg/m²/day + FOL 20 mg/m²/day × 5 days (2 cycles)</td>
<td>32% versus 78% (WHO grade 2–4; P = 0.001) 3.4 versus 10.2 (WHO grade 2–4; P = 0.001)</td>
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<tr>
<td>Meropol et al. 2003 [87]</td>
<td>1–80 μg/kg/day × 3 per cycle (pre)</td>
<td>Metastatic colorectal (81)</td>
<td>–</td>
<td>5-FU 425 mg/m²/day + FOL 20 mg/m²/day × 5 days (2 cycles)</td>
<td>43% versus 67% (WHO grade 2–4; P = 0.06)</td>
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*Phase I/II studies were not primarily designed to evaluate efficacy, but efficacy data are included here for interest.

°Results are shown for palifermin 60 μg/kg × 3 days.

5-FU, 5-fluorouracil; BEAM, carmustine, etoposide, cytarabine, melphalan; CYC, cyclophosphamide; ETO, etoposide; FOL, folic acid; HSCT, haematopoietic stem-cell transplantation; WHO, World Health Organisation.

high-dose chemotherapy ± radiotherapy + autologous HSCT
A phase I–II dose-ranging study was conducted in patients with haematological malignancies undergoing BEAM (carmustine, etoposide, cytarabine, melphalan) chemotherapy followed by autologous HSCT. A 60 μg/kg/day was found to be the optimal dosage [84] and was subsequently evaluated in a phase II [85] and a phase III [22] study in patients undergoing HSCT (Table 1). Patients in both studies received total body irradiation (TBI; 12 Gy) and high-dose chemotherapy (etoposide 60 mg/kg and cyclophosphamide 75 or 100 mg/kg) as a conditioning regimen, with filgrastim 5 μg/kg/day until neutrophil recovery [22, 85].

Results from the phase II study (n = 129 patients) showed that a three-dose ‘pre’ (pre-chemotherapy) and a six-dose ‘pre/post’ regimen were both effective in reducing the duration of severe oral mucositis and its sequelae (Table 1). Thus, the mean duration of mucositis was reduced from 7.7 days for placebo to 5.0 days (P < 0.04) with the three-dose regimen and 4.0 days (P < 0.001) with the six-dose regimen [85].

Thus, the pivotal phase III study evaluated palifermin 60 μg/kg/day pre/post [22]. Compared with placebo, palifermin...
significantly ($P < 0.001$) reduced both the incidence and median duration of severe (WHO grade 3/4) oral mucositis, from 98% (104/106) to 63% (67/106) of patients and from 9.0 (range 1–27) to 6.0 (range 1–22) days (Figures 3 and 4). Importantly, the incidence and median duration of grade 4 mucositis (which precludes any oral alimentation) were reduced from 62% to 20% of patients ($P < 0.001$) and from 6.0 (range 1–37) to 2.0 (range 1–9) days ($P = 0.004$).

Patient-reported mouth and throat soreness was also significantly reduced (by 38% versus placebo; $P < 0.001$) in palifermin recipients, resulting in improved scores for daily activities, such as swallowing, eating, talking and sleeping, and for physical and functional well-being, as assessed by the Functional Assessment of Cancer Therapy general questionnaire [22]. Consequently, palifermin recipients required significantly less IV/transdermal opioid analgesics, in terms of both dosage (212 versus 535 mg median cumulative morphine equivalent) and median duration (7.0 versus 11.0 days), less TPN (31% versus 55% of patients; $P < 0.001$ all comparisons) [22] and a shorter hospital stay (15.3 versus 17.3 days; $P = 0.008$) [88]. Additionally, significantly fewer palifermin recipients experienced febrile neutropenia (75% versus 92% of patients; $P < 0.001$), with a concomitant trend towards a lower incidence of blood-borne infections (15% versus 25% of patients) [22]. These data suggest that palifermin may help to preserve mucosal barrier function in patients undergoing myelotoxic-conditioning regimens.

### Multicycle Chemotherapy for Solid Tumours

When given as a three-dose regimen before fluorouracil/folinate chemotherapy in patients with advanced colorectal cancer, palifermin reduced the incidence of WHO grade 2–4 oral mucositis [86, 87]. In a phase I study ($n = 81$), patients treated with palifermin in dosages ranging from 1 to 80 μg/kg/day experienced a lower incidence of mucositis than placebo recipients, although the difference did not quite attain statistical significance (43% versus 67%; $P = 0.06$). Exploratory analyses revealed a trend towards a reduction in the incidence of grade 2–4 oral mucositis in those who received palifermin at doses $\geq 10 \mu g/kg/day$ [87]. A subsequent phase II study ($n = 64$) found that palifermin 40 μg/kg/day reduced the incidence of mucositis over two cycles of fluorouracil/folinate chemotherapy, from 78% to 32% of patients ($P = 0.001$) [86].

### Tolerability

Palifermin appears to be well tolerated at the dosages studied. Adverse events are generally consistent with the biological activities of this growth factor, consisting mainly of skin and/or oral erythema with or without oedema. Transient, asymptomatic increases in serum amylase and lipase also occur [22, 85–87]. A maximum tolerated dose, as per predefined criteria, was not reached in a phase I study in patients with colorectal cancer [87]. Nevertheless, dose escalation was halted at 80 μg/kg/day $\times$ 3 doses because of grade 2–3 cutaneous toxic effects, requiring discontinuation of treatment, experienced by three palifermin recipients. Oral and cutaneous toxic effects were generally mild to moderate and were dose-related, occurring in 13 of 18 patients treated with palifermin 60 or 80 μg/kg/day (eight grade 1, four grade 2 and one grade 3) and 3 of 11 patients receiving 40 μg/kg/day (all grade 1). Increases in serum amylase and lipase were also more pronounced at the higher dose levels [87].

In the phase III study, rash, pruritus, erythema, cough and oedema were the most common events reported by palifermin recipients, occurring in 55%, 50%, 44%, 32% and 27% of patients, respectively. However, these events were also relatively common in the placebo group, with corresponding incidences of 46%, 32%, 30%, 26% and 17%, respectively. All events were transient and mild to moderate and none led to discontinuation of palifermin treatment. Anti-palifermin antibodies were not detected [22].

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**Figure 3.** Incidence of oral mucositis following myelotoxic conditioning treatment before haematopoietic stem cell transplantation in patients treated with palifermin 60 μg/kg/day compared with placebo recipients. Figure reprinted from Spielberger et al. (2004) [22] with permission.

**Figure 4.** Median duration of grade 3–4 mucositis following myelotoxic conditioning treatment before haematopoietic stem cell transplantation in patients treated with palifermin 60 μg/kg/day ($n = 106$) compared with placebo recipients ($n = 106$) [22].
Given that many epithelial cancers express the KGF receptor, and the reported effects of palifermin on apoptotic pathways, there are concerns that it might compromise the effects of chemotherapy or radiotherapy. As haematological cancers do not express the KGF receptor [89], it seems unlikely that palifermin would have any adverse effects on outcome in this type of malignancy, although growth of second tumours that express this receptor is theoretically possible. A recent analysis of the long-term effects of palifermin in patients with haematological malignancies found that the rates of overall and progression-free survival, disease progression and second malignancies were similar between palifermin (n = 409) and placebo (n = 241) recipients during a median follow-up period of approximately 2 years [90].

Palifermin did not appear to stimulate growth of various solid tumours or compromise the tumour growth inhibitory effects of chemotherapy or irradiation, in vitro or in vivo [49, 91]. Although KGF promoted proliferation in human endometrial carcinoma cells, via activation of the MAPK pathway, the effect was small [92]. Few clinical data are available regarding the use of palifermin in solid tumours. Median survival was comparable for palifermin and placebo groups (71 versus 66 weeks) in patients with advanced colorectal cancer (n = 64) [86].

discussion

Myelosuppression was previously the dose-limiting toxicity for the majority of intensive cancer therapies. However, with the advent of growth factors for haematopoietic support and improved transplantation procedures, nonhaematological toxic effects such as mucositis have now become dose-limiting. Indeed, the development of new options to treat and prevent mucositis in patients undergoing chemotherapy and radiotherapy has been a priority in oncological supportive care. Amelioration of mucositis in such patients can potentially reduce associated morbidity, mortality and healthcare resource utilisation, as well as improving patients’ QoL and allowing optimally effective treatment schedules to be given.

Recent research has shown that MBI is a complex and dynamic process that targets the endothelial cell and connective tissue, as well as the epithelium itself, manifesting not only in the oral cavity but throughout the alimentary tract. Further work is needed to refine the five-stage model of mucositis described in this article and identify the key factors involved and this may lead to further advances in treatment. It seems clear that effective agents will be those that are pleiotropic in their ability to modulate the complex pathogenic mechanisms that drive MBI. Reliable, standardised markers are also needed to evaluate intestinal mucositis in the clinical setting. While sugar permeability tests are a noninvasive means of measuring the altered permeability and loss of epithelial surface that characterises gut MBI, these are cumbersome and rely on patient compliance. Recently it has been shown that plasma citrulline, a reliable biomarker of small bowel enterocyte mass in patients with conditions associated with villous atrophy, provides an objective, sensitive and specific parameter for measuring gut MBI [93]. It is hoped that this new tool will allow further exploration of the relationship between intestinal MBI and complications of cancer treatment.

While choice of regimen and patient factors, such as age, gender and nutritional status, influence the risk of mucositis, it is not yet possible to identify those individuals who are at high risk of developing severe mucositis. Recent data have implicated polymorphisms in genes involved in the metabolism of chemotherapeutic agents that result in higher tissue drug concentrations [94, 95]. Genes that regulate production of cytokines involved in tissue injury may also be important. The identification of mechanistically related single nucleotide polymorphisms might provide a cost-effective methodology for risk prediction in the future.

Palifermin represents the first agent to be approved for the prevention of oral mucositis. This pleiotropic growth factor offers within a single molecule multiple biological activities that target several stages of the mucositis process (Figure 5). It has proven efficacy in ameliorating oral mucositis in patients undergoing high-dose chemotherapy and TBI prior to HSCT. Clinical sequelae, including febrile neutropenia and resource use (opioid analgesia and parenteral feeding), are concomitantly reduced. Palifermin has also shown promise in those receiving multicyle chemotherapy for colorectal cancer and is currently being evaluated in other solid tumour settings, including head and neck cancer, non-small-cell lung cancer and sarcoma (http://www.clinicaltrials.gov). The optimal palifermin dose and schedule need to be defined for these settings. Palifermin has been well tolerated in clinical trials to date. However, data regarding its potential impact on the efficacy of cancer treatments are required, particularly in patients being treated for solid tumours.

Data from animal models suggest that palifermin may prevent intestinal mucositis induced by chemotherapy and/or radiotherapy [49, 54]. Prevention of gut MBI may be critical for attenuating GVHD in patients undergoing allogeneic BMT/HSCT and the concept of protective ‘cytokine shields’ has been proposed in this setting [13]. Epithelial cells appear to be the principal targets of acute GVHD, which is largely mediated by Th1 cytokines, particularly IFN-γ, secreted by host-reactive donor T cells [96]. However, attempts to reduce GVHD by elimination of donor T cells from the graft can result in poor engraftment and loss of graft-versus-leukaemia effects. Palifermin has shown interesting potential as an adjunct to standard GVHD prophylaxis in patients undergoing allogeneic transplantation. In preclinical models of allogeneic BMT, it prevented GVHD and associated mortality [68, 97, 98], with a concomitant reduction in serum LPS [68] and preservation of donor T cells and graft-versus-leukaemia effects [68]. These effects appear to be independent of repair of conditioning-induced tissue injury, as palifermin also reduced GVHD associated with T-cell transfer in severe combined immunodeficient mice [69] or nonconditioned [70] or nonmyeloablative haploidentical [98] transplantation. Palifermin also prevented idiopathic pneumonia syndrome, a further complication of BMT [71]. In a phase I study in patients undergoing unrelated or mismatched donor transplant following a fully myeloablative conditioning regimen (a population at high risk of GVHD), palifermin treatment reduced the incidence of grade 3–4 GVHD from 35% (seven of 20 patients) to 20% (three of 15 patients) and the mortality rate from 30% to 14% at 100 days [99]. Moreover, in animal studies
palifermin protected against thymic epithelial cell injury and improved T-cell reconstitution after sublethal irradiation or chemotherapy [100], or various transplantation protocols [100–103].

Thus, the development of palifermin and other potential new agents for preventing mucositis caused by chemotherapy and radiotherapy in cancer patients represents an important breakthrough in oncological supportive care. It is hoped that continuing research will allow this condition to become a preventable complication of cancer treatment. Palifermin has multiple biological activities that validate the concept of a pleiotropic agent for mucositis and it appears likely to find other clinical applications in the future.

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Figure 5. Summary of postulated mechanisms by which palifermin may ameliorate chemotherapy- and radiotherapy-induced mucositis (adapted from Sonis et al. 2004) [55]. ↑ = increased/up-regulated; ↓ = decreased/down-regulated; ROS, reactive oxygen species.


