Current concepts in the pathogenesis and management of oral mucositis as a complication of cancer therapy

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Abstract

The ubiquitous nature of oral mucositis in patients undergoing chemotherapy, radiotherapy and bone marrow transplantation and its effect on patient quality of life, coupled with notable recent advances in better understanding of the pathobiology of mucositis, have brought about a shift from the symptomatic approach in management to a preventive one. This has been reflected in the literature over the past five years or so, and has culminated in the introduction of a variety of new medications, the majority of which are still being investigated. A universal management scheme for oral mucositis is far from being realised, but the current management guidelines as developed by the Multinational Association of Supportive Care in Cancer is invaluable for clinicians of all disciplines involved. The introduction of the recently-approved human recombinant keratinocyte growth factor (palifermin) is perhaps one of the most notable achievements in mucositis research; but the possibility of a topical preparation and its potential in other disease conditions have not been tapped into as yet.

Key words: Oral mucositis, chemotherapy, radiation therapy, management, keratinocyte growth factor, palifermin

Introduction

Oral mucositis occurs with a prevalence of about 40% in standard-dose anti-cancer regimens (Karhaus et al., 1999). Along with xerostomia, it is the most common side-effect of anti-neoplastic therapy. It is characterised by pain, erythema, ulceration and sometimes bleeding, starting shortly after treatment is initiated and resolving usually within a few weeks. Oral mucositis can have a profound effect on patients’ quality of life, interfering with eating, speaking, swallowing and other daily functions. Narcotic analgesia is often used in severe cases (Wardley et al., 2000).

Diagnosis of oral mucositis is clinical, and several scoring systems exist (Parulekar et al., 1998). The most widely used of these is the grading scale proposed by the World Health Organisation which incorporates both objective criteria according to the clinical appearance of lesions and subjective parameters that correlate with patient symptoms (Stiff et al., 2006a). Considering how common the condition is in anticancer therapy, it remains an under-researched area and there remains no consensus in terms of management, with a lack of universal guidelines or management strategies. Nevertheless, it is generally accepted and recommended by the Multinational Association of Supportive Care in Cancer that a high standard of oral health should be the aim before the commencement of anti-cancer therapy (Biron et al., 2000; Djuric et al., 2006; Sonis et al., 2004).

An electronic Medline search supplemented by a manual search of the literature from September 1989 to April 2007 was performed using the terms ‘oral mucositis’, ‘palifermin’ and ‘keratinocyte growth factor’. Assessment of articles for selection was done independently by the two reviewers. Articles that emphasised the therapeutic modalities of oral mucositis were reviewed.

Aetiopathogenesis

Whereas an earlier model of the pathogenesis of mucositis attributed the process to direct epithelial injury, placing little or no importance on the role of pro-inflammatory cytokines, it has now emerged that the precise aetiology of mucositis is far more complex, with a multifactorial background in which submucosal injury precedes epi-
The five phases of mucositis according to Sonis et al. (2004) are initiation, upregulation, signal amplification, ulceration and healing. The initial phase is characterised by chemotherapy and radiotherapy-induced direct breaks in DNA strands in basal epithelium, causing the release of reactive oxygen species, which result in direct damage to the cells, causing clonogenic cell death (Figure 1). This is followed by the production and release of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) causing tissue damage and apoptosis. A key element in this process is nuclear factor-κB which upregulates the aforementioned cytokines and thus plays a key role in the apoptotic pathway of mucositis (Rubenstein et al., 2004). Reactive oxygen species may also stimulate the formation of sphingomyelinase and/or ceramide synthase, which activate the ceramide pathway leading to apoptosis. Pro-inflammatory cytokines then amplify the damage initiated by radiation and chemotherapy via a positive feedback mechanism (Figure 2). The ultimate result of these metabolic activities is tissue ulceration. This is the most notable stage clinically as it results in severe pain for the patient. Colonising micro-organisms invade the submucosa, activating macrophages, which promote the release of further pro-inflammatory cytokines (Figure 3). Finally, the extracellular matrix signals renewal with epithelial cell proliferation and differentiation. This coincides with the return of neutrophils to their normal levels in the peripheral circulation, approximately two weeks after the initial insult (Sonis, 2004; Silverman, 2007).

Figure 1: Initiation phase of mucositis (derived from Sonis, 2004)
Clinical features of oral mucositis

Oral mucositis due to chemotherapy typically starts 5-7 days after the initiation of treatment in the form of erythema affecting the non-keratinised oral tissues: the soft palate, ventral surface of the tongue, buccal mucosa and floor of the mouth. This is frequently followed by oedema and ulceration (Figures 4 and 5), ranging from ulcerative lesions to generalised desquamation, peaking on days 11-14 (Karthaus et al., 1999). High-dose radiation therapy of about 15-20Gy affects all soft tissues within its field. Consequently, no oral site is spared (Redding, 2005).

Basal cell regeneration and healing normally begin 9-14 days after injury and this is also associated with the re-establishment of a normal oral bacterial flora. However, chronic injury, including persistent xerostomia and a subsequent predisposition to dental caries is not uncommon (Barasch and Peterson, 2003).

Current concepts in the management of oral mucositis

There have been numerous attempts at formulating a management protocol for mucositis but with little agreement, mainly due to conflicting and non-standardised parameters used in evaluating new drugs (Barasch and
and Peterson, 2001; Stiff, 2001). However, the management guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC) in collaboration with the International Society for Oral Oncology are of paramount importance for clinicians from all disciplines that are involved in the management of mucositis. Table 1 (Rubenstein et al., 2004) shows a summary of some of the therapeutic modalities investigated in the management of oral mucositis.

**Growth factors**

This group of drugs is the latest addition to mucositis-related research and seems to be the area receiving the most intense amount of interest currently. Recombinant forms of epidermal growth factor (EGF), granulocyte colony stimulating factor (GCSF), granulocyte macrophage colony stimulating factor (GMCSF) and, most significantly, keratinocyte growth factor (KGF) seem to be at the centre of current studies.

**Keratinocyte growth factor (KGF)**

This is probably the most notable therapy added to the management strategies for mucositis in recent years. KGF is a naturally occurring, 28 kDa heparin-binding member of the fibroblast growth factor family, binding to its receptor on a variety of epithelial tissues including skin keratinocytes and stratified squamous epithelium, gastrointestinal and oral epithelial cells, hepatocytes and type II pneumocytes (Danilenko, 1999). It stimulates DNA synthesis in a variety of tissues, and its affects are maximal on the oral mucosa and the upper digestive tract. After animal studies yielded favourable results (Dorr et al., 2002), clinical trials of recombinant human keratinocyte growth factor in humans produced positive outcomes (Antin et al., 2001; Brizel et al., 2001; Durrant et al., 1999; Meropol et al., 2003; Serdar et al., 1997).

<table>
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<tr>
<th>Table 1. Summary of MSACC clinical practice guidelines for care of patients with oral mucositis (Rubenstein et al., 2004)</th>
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<tr>
<td>Oral care protocols: e.g. plaque removal, chlorhexidine 0.2% mouthwash, patient education</td>
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<tr>
<td>Patient-controlled analgesia with morphine in patients undergoing haematopoietic stem cell transplantation</td>
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<tr>
<td>The use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury</td>
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<tr>
<td>Chlorhexidine is not recommended as a preventative agent for oral mucositis</td>
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<tr>
<td>Thirty-minute cryotherapy in patients undergoing 5-fluorouracil chemotherapy</td>
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<tr>
<td>Acyclovir and its analogues are not recommended for routine use in prevention of oral mucositis</td>
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<tr>
<td>In centres capable of supporting the necessary technology and training, low level laser therapy is recommended to reduce the incidence of oral mucositis</td>
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**Figure 4: Mucositis on the lateral border of the tongue**

**Figure 5: Mucositis on the posterior buccal mucosa**
The pivotal phase II study by Spielberger et al. in 2004, in which 106 patients received palifermin (an N-terminal, truncated version of endogenous KGF with biological activity similar to that of the native protein) concluded that administering 60μg of palifermin per kilogram per day, parenterally over 3 days, before the commencement of antineoplastic therapy was associated with reductions in the duration and severity of oral mucositis and the related sequelae of high-dose myelosuppressive treatment with autologous haematopoietic stem-cell support. All adverse reactions were consistent with the pharmacologic action of palifermin on skin and oral mucosa, those being pruritus, erythema, paraesthesia and altered taste. Results from a phase III trial concluded that patients receiving palifermin saw improvements in their daily activities and physical and functional well-being (Stiff et al., 2006b).

Palifermin has recently been approved by the FDA for the treatment of mucositis in patients undergoing treatment for haematological malignancies. The full potential of palifermin is far from being fully explored, and its safety and efficacy in nonhaematological malignancies have not been established (Speilberger et al., 2004). There have been no studies as yet exploring the possibility of a topical preparation of palifermin and its potential as a treatment for oral mucositis or, indeed, oral ulceration due to other causes.

**Transforming growth factor-β (TGF-β3)**

A human recombinant form of TGF-β3 has been developed and shown to inhibit reversibly, the cycling of epithelium, including human buccal mucosa. Topical administration of TGF-β3 to the oral cavity was shown to reduce the severity of mucositis in patients after 5-Fluororacil administration. However, other studies found that the application of TGF-β3 may actually worsen the clinical course of mucositis. These conflicting reports have led to its withdrawal from further clinical development for oral mucositis (Trotti, 1998).

**Colony-stimulating factors**

The use of these glycoproteins is based upon the fact that they stimulate proliferation on nonhaematopoietic tissues. The rationale behind their use is also correlated to the fact that mucositis resolves around the same time as the levels of peripheral neutrophils return to normal. Clinical trials investigating the topical use of GM-CSF in the form of a mouthwash has yielded no evidence to support its use (Makkenon, 2000; Valcarcel et al., 2002).

**Epidermal Growth Factor (EGF)**

Radiation therapy results in the reduction of salivary EGF flow, a molecule that plays a role in wound healing. Studies have shown conflicting results in terms of the relationship of higher levels of salivary EGF with more or less severe mucositis (Wardley, 2000). A phase I clinical trial on EGF mouthwash concluded that it does not accelerate ulcer healing, but it may have the potential to protect the oral epithelium from cytotoxic damages (Girdler et al., 1995).

**Amifostine**

Amifostine (Ethylol) is an inorganic cytoprotector that has been investigated for its protective effects against oral mucositis, xerostomia and other anti-cancer therapy when given in the dose of 200mg/m2 intravenously. Despite success in preventing mucositis in animal models, Ethylol seems to be more useful in reducing the severity of anti-cancer therapy-associated xerostomia rather than oral mucositis (Brizel et al., 2003; Cassatt et al., 2005; Koukourakis, 2002; Wasserman et al., 2000). **Oral hygiene measures and mouthwashes**

Data are conflicting on the effectiveness of oral care in reducing the severity of oral mucositis. Several studies have shown a reduction in mucositis in patients who received oral care to remove sources of infection before and during their cancer therapy, whilst other studies have shown no such changes. Nevertheless, oral hygiene measures in the form of soft-bristled toothbrushes, dental floss and mouthwashes is recommended (Djuric et al., 2006; Scully and Epstein; 1996; Scully, Epstein and Sonis, 2004). Controlled trials have been performed with a number of agents including hydrogen peroxide and chlorhexidine (Epstein et al., 1992; Wahlin et al., 1989) but in general they have not led to a significant improvement in oral mucositis— in fact, some studies have pointed out detrimental effects when using chlorhexidine (Foote et al., 1994). The use of benzydamine hydrochloride, a mouthwash with anaesthetic and analgesic qualities has similarly not yielded any tangible results (Epstein et al., 2001); however, currently the MSACC recommends the use of benzydamine mouthwash as a preventative measure for oral mucositis in patients receiving radiotherapy to the head and neck (Sonis et al., 2004).

Sucralfate is a basic aluminium salt used in the treatment of peptic ulcers that has occasionally proven to be of use in the management of oral mucositis. However, controlled clinical trials have shown that sucralfate is ineffective for the prevention or management of mucositis (Dodd et al., 2003; Nottage et al., 2003).

Mouthwash preparations containing allopurinol, a xanthine-oxidase inhibitor used in the treatment of gout and considered to have a cytoprotective effect in epithelium against antineoplastic therapy, have also proven to be of little use in oral mucositis (Loprinzi et al., 1990; Porta et al., 1994). Cocaine mouthwash is frequently prescribed but
there have been no controlled clinical trials to fully explore its mechanism of action and potential side-effects.

**Cryotherapy**
The mechanism by which this works is reducing blood flow to the oral mucosa during chemotherapy administration by virtue of local vasoconstriction action. Ice chips are placed in the mouth for 5 minutes before bolus administration, and then for a further 25 minutes afterwards. Cryotherapy seems to be particularly effective in the treatment of oral mucositis associated with 5-fluorouracil therapy (Karagozoglu and Filiz Ulusoy, 2005; Nikoletti, 2005). Thirty-minute cryotherapy sessions for patients undergoing treatment under 5-FU chemotherapy is the current recommendation according to the guidelines of the MSACC (Sonis et al., 2004).

**Interleukin 11**
This cytokine ameliorates thrombocytopenia in the aftermath of myelosuppressive chemotherapy. Other actions, demonstrated in vitro, suggest its potential value in the modulation of mucositis (Karthauser et al., 1999). A randomised, placebo-controlled study explored doses of IL-11 along with high-dose chemotherapy with favourable results. A clinical trial using IL-11 50µg/kg daily subcutaneously did not provide favourable results (Danilenko, 1999). Further studies are needed to fully evaluate the potential use of IL-11 for oral mucositis (Sonis et al., 1999).

**Nutritional supplements**
Glutamine is an amino acid that plays a significant role in maintaining the integrity of oral and intestinal mucosa. Clinical trials to investigate a 500mg/ml glutamine suspension with a daily dose of 4 or 8mg have reduced the severity of the condition but have not succeeded in preventing it (Anderson et al., 1998; Huang et al., 2000; Worthington et al., 2004).

**Other products under development**
Meclocycline sulfosalicylate is a broad spectrum antibiotic that has been used for the management of acne vulgaris. A mouthrinse preparation of this agent (SNX-1012; formerly known as OC-1012) yielded favourable results and exhibited a safe profile in Phase I trials on bone marrow transplant patients undergoing chemotherapy. Phase II clinical trials are currently underway and are expected to continue into 2008 [unpublished data].

**Conclusion**
There have been major steps recently in unveiling the aetiological pathway involved in oral mucositis which have culminated in a major shift in the management of the condition from treatment of symptoms to prevention. The use of the recently-approved human recombinant keratinocyte growth factor (palifermin) has proven to be particularly promising; however, its substantial cost presents itself as an important factor to consider. The potential use of keratinocyte growth factor in the treatment of other forms of oral disease also remains an unexplored avenue.

**References**


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