

## Topical Agents for the Management of Oral Complications in Cancer Patients

a report by

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Cancer patients commonly suffer from oral complications during and following cancer therapy. These include oral/pharyngeal mucositis (OM), infection, pain, bleeding, and hyposalivation. In addition, rampant dental caries may develop in patients treated with radiation in the head and neck region (H&N RT). Patients treated with hematopoietic stem cell transplant (HCT) may develop oral graft versus host disease (GVHD).

Approximately 1.2 million Americans receive cancer therapy each year, of whom approximately a third develop OM. It is the most common debilitating acute complication of cancer chemotherapy and H&N RT reported by patients, and is among the most significant major dose-limiting toxicities of cancer therapy. Severe OM may result in dose reduction, dose delay, and even in termination of planned therapy. In addition, OM is associated with considerable cost implications, ranging from US\$12,000 in patients with solid tumors to US\$42,000 in HCT patients.

In radiation-induced OM, initial mucosal whitening may occur prior to erythema and mucosal ulceration. Mucosal lesions that extend beyond the field of radiation often represent infection due to candidiasis or herpes simplex virus (HSV) reactivation. In contrast, chemotherapy-associated OM typically presents bilaterally. Myelo-suppression increases the risk of bacterial and fungal invasion and systemic infection. Generally, three to five weeks are required for oral tissues to heal following completion of H&N RT, whereas healing typically occurs in two to three weeks after cancer chemotherapy.

The pathogenesis of OM is complex, involving cells of connective tissue and epithelium. Bacterial colonization of mucosal lesions and exposure of submucosal tissues to lipopolysaccharide may contribute to the severity of mucositis. It is important to further identify the sequence of the cellular and tissue events involved because this may provide a key to adequate prevention and treatment.

The risk factors for OM have not been well established, although high-risk cancer treatment protocols are defined. A number of variables have been suggested to increase the risk of mucositis, which include poor oral hygiene, trauma, tobacco use, hyposalivation, lower

baseline neutrophil counts, impaired renal function, genetic polymorphisms, body mass, gender, and old age. However, study design deficiencies have hampered mucositis prevention trials and affected acceptance of the results of these studies.

The protective and homeostatic role of saliva has been documented. Important salivary functions include physical cleansing of the oral cavity, facilitation of deglutition and speech, antimicrobial activities, and buffering of acidic bacterial metabolic by-products. H&N RT leads to irreversible damage to salivary glands that are in the high-dose volume. Dry mouth (xerostomia) is a common complaint in patients on chemotherapy. In HCT patients, total body irradiation (TBI), as well as chronic GVHD, may contribute to hyposalivation. Hyposalivation predisposes to dental caries, periodontal diseases, mucosal infection, mucosal trauma (e.g. denture irritation), reduced denture retention, altered speech and taste, and inability to take certain foods by mouth.

Loss of barrier function and salivary dysfunction enhances the risk for oral and systemic infection, particularly in myelo- and immuno-suppressed patients. Malignant disease, antibiotic regimens, and cancer treatment may impair the equilibrium between the oral microflora and the host. This leads to an increased risk for infection by micro-organisms that are part of the normal flora, and also promotes a shift in favor of pathogenic gram-negative bacteria. The most common oral bacterial infection in neutropenic patients is caused by streptococci, which often translocate into the bloodstream particularly in the presence of ulcerative OM. Although the majority of patients with viridans streptococcal bacteremia have no other manifestation of infection than fever, some patients develop an acute respiratory distress syndrome (ARDS) and septic shock, especially following bacteremia with *S. mitis*. In addition, systemic and invasive fungal infection is of concern. Whereas oropharyngeal candidiasis is associated with symptomatic infection, diagnosis of systemic candidiasis is difficult.

Cancer patients can experience mild to excruciating oropharyngeal pain induced by a variety of causes. OM is by far the most frequent cause and may necessitate the prescription of opioid analgesics.

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Oral infection is also a common cause of oral symptoms. Reactivation of latent viruses such as herpes simplex (HSV) and varicella zoster is often painful. In addition, acute necrotizing gingivitis and exacerbation of chronic dental infections are associated with pain. Furthermore, solid oral tumors, leukemia, multiple myeloma, or metastatic breast cancer may be associated with oral and facial numbness and pain.

Topical approaches to prevention and management of oral complications offer the potential advantages of high local concentration with limited or no systemic penetration and with reduced risk of drug interactions and toxicity. A number of the conditions of concern in cancer patients occur on the mucosal surface (e.g. candidiasis), and in the epithelium and immediately adjacent connective tissue (e.g. mucositis), and therefore are amenable to topical therapies.

Topical therapy requires a means of delivery of the medication to the site, retention, and release of the medication. Different forms of delivery include rinses, topical gels or creams, lozenges, and chewing gum. Selected currently used topical treatment approaches, and the need to develop products in formulations acceptable to cancer patients and to conduct studies in these patient populations, will be discussed.

### Basic Oral Care

Excellent oral hygiene should be promoted to reduce the oral bacterial load and decrease the risk of caries and periodontal diseases. There is some evidence that good oral hygiene is associated with less severe OM. However, there is no universally recommended oral care protocol. In addition, trauma to the oral tissues should be avoided.

### Oral Mucositis

Bland oral rinses are commonly recommended; however, evidence of effectiveness in reducing OM is lacking. A study comparing saline and hydrogen peroxide rinses during H&N RT found no differences in OM, although oral sensitivity was greater in those using peroxide. The literature supports using ice chips (cryotherapy) for short half-life stomatotoxic chemotherapy delivered by bolus injection.

Coating agents have been used as vehicles and as topicals to cover damaged mucosa. These include sucralfate, kaopectate, milk of magnesia, amphojel, hydroxypropyl methylcellulose film-forming agents, and Gelclair®.

Sucralfate, an aluminum salt of sucrose octasulfate, is a cytoprotectant that has been studied in OM associated with chemotherapy, radiation, and HCT. It is thought to adhere to ulcer bases, thus creating a surface barrier in

the gastrointestinal tract. In addition, sucralfate may have some antibacterial activity and may accelerate wound healing. While less severe OM has been reported in some trials, numerous others have found no benefit. Another hypothesized benefit of sucralfate use is reduced mucosal adherence of potentially pathogenic oral organisms in patients with OM, but no proof of this effect on infectious outcomes has been reported.

Antimicrobial therapy has long been considered as an OM intervention. A reduction in the bacterial load on the surface of ulcerative lesions would seem of benefit in assuring that secondary infection does not interrupt ulcer healing. However, there are no consistent data to support the use of antimicrobials as a primary mucositis therapy.

Chlorhexidine rinses have been subject to a number of clinical trials for prevention of OM. While the potential value of chlorhexidine for controlling chemotherapy-associated OM was reported in some studies, this finding has not been universal. Chlorhexidine has been shown to have no effect upon radiation OM. The benefits of rinsing with chlorhexidine are control of dental plaque levels and reducing gingivitis, caries risk, and oropharyngeal candidiasis, rather than prevention of OM. The acceptance of chlorhexidine oral rinses in patients with OM is limited because the alcohol and flavoring agents generally used in these rinses can be painful, although aqueous solutions may be better accepted.

Studies evaluating the potential of a non-absorbable antimicrobial lozenge combining polymixin, tobramycin, and amphotericin B (PTA) to prevent or ameliorate OM report mixed results. Although a large single-center study using PTA reported a reduction in radiation-induced OM in the lozenge arm, another double-blind multi-center study on PTA found no effect. Other randomized single-center studies on PTA and H&N RT or chemotherapy-induced OM also reported negative or modest results. Isegenan is an antimicrobial peptide that has been reported to ameliorate chemotherapy-induced OM in a phase III study; a larger multi-center phase III study on H&N RT patients failed to show reduction of OM. A prospective study on povidone-iodine rinses in patients treated with chemoradiotherapy for head and neck cancer reported reduced severity and duration of OM.

Growth factors and cytokines have pluripotential effects. Time of administration, dose, concentration, and duration of contact in the oral environment may affect the outcome. A number of studies have examined the potential benefit of the hematopoietic growth factors to prevent OM, but have shown inconsistent results. A placebo-controlled trial on topical granulocyte colony stimulating factor (G-CSF) in patients receiving chemotherapy for non-Hodgkin's lymphoma reported

a trend to less severe OM. Several preliminary studies have assessed granulocyte-macrophage colony stimulating factor (GM-CSF) mouth rinses on oral mucositis, and less severe or reduced duration of OM was seen in several trials. However, a double-blind, placebo-controlled study of GM-CSF mouth rinse conducted in 45 patients receiving chemotherapy showed no reduction in mucositis.

Epidermal growth factor (EGF) may represent a marker of mucosal damage and has the potential to promote resolution of radiation-induced OM. A preliminary study in head and neck cancer patients showed increase of OM in patients with higher levels of EGF in saliva. However, in a larger study, higher EGF salivary levels were associated with less severe OM. A double-blind trial of EGF mouthwash in patients treated with chemotherapy showed no differences in the healing of established ulcers, but a delay in onset and reduced severity was seen in recurrent ulceration, suggesting that topical EGF may protect the mucosa.

Transforming growth factor beta 3 (TGF- $\beta$ 3), which reduces epithelial cell proliferation, reduced the incidence, severity and duration of mucositis when given after chemotherapy in animal studies. Clinical

trials with this agent suffered from dosing concerns and results were mixed. Interleukin (IL)-11 demonstrated efficacy in reducing both experimental and clinical OM. IL-11 was shown to modulate gene expression responsible for tumor necrosis factor alpha (TNF- $\alpha$ ) in irradiated mucosa.

Similarly, benzydamine HCl has anti-TNF- $\alpha$  capacity. This non-steroidal anti-inflammatory agent has been shown to reduce the severity of OM during radiation therapy and to reduce oral pain. Benzydamine is available in many countries and is currently in phase II trial in the US.

Amifostine is a thiol compound shown in animal studies to protect a variety of tissues when administered prior to irradiation. Systemic amifostine is indicated for salivary gland protection during radiation therapy and it may reduce OM. Pre-clinical studies showed reduction of radiation-induced OM after local application of amifostine, whereas a recent study on non-small-cell lung cancer patients failed to show clinically detectable reduction of OM. ■

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