

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 chemotherapy¹ and H&N RT² reported by patients, and is among the most significant major dose-limiting toxicities of cancer therapy.³⁻⁶ 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^{7,8} to US\$42,000 in HCT patients.⁹

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. Myelosuppression 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.^{10,11} 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.¹²⁻¹⁵ 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.^{16,76} Dry mouth (xerostomia) is a common complaint in patients on chemotherapy.¹⁷ 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 immunosuppressed 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.¹⁸ 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.¹⁹⁻²¹ 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*.^{22,23} In addition, systemic and invasive fungal infection is of concern.²¹ Whereas oropharyngeal candidiasis is associated with symptomatic infection, diagnosis of systemic candidiasis is difficult.



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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.^{24,25}

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.²⁶⁻²⁸ In addition, trauma to the oral tissues should be avoided.²⁹

Oral Mucositis

Bland oral rinses are commonly recommended; however, evidence of effectiveness in reducing OM is lacking.³⁰ 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.³¹ The literature supports using ice chips (cryotherapy) for short half-life stomatotoxic chemotherapy delivered by bolus injection.³²

Coating agents have been used as vehicles and as topicals to cover damaged mucosa. These include sucralfate, kapectate, milk of magnesia, amphojel,

hydroxypropyl methylcellulose film-forming agents, and Gelclair®.³³

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.³⁴⁻³⁷ 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.³⁴

Anti-microbial 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,^{38,39} this finding has not been universal. Chlorhexidine has been shown to have no effect on radiation OM.⁴⁰ 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 anti-microbial 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,⁴¹ another double-blind multi-center study on PTA found no effect.⁴² Other randomized single-center studies on PTA and H&N RT or chemotherapy-induced OM also reported negative or modest results.⁴³⁻⁴⁵ Isegenan is an anti-microbial peptide that has been reported to ameliorate chemotherapy-induced OM in a phase II study;⁴⁶ a larger multi-center phase III study on H&N RT patients failed to show reduction of OM.⁴⁷ A prospective study on povidone-iodine rinses in patients treated with chemoradiotherapy for head and neck cancer reported reduced severity and duration of OM.⁴⁸

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.⁴⁹ 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.^{50,51} However, a double-blind, placebo-controlled study of GM-CSF mouth rinse conducted in 45 patients receiving chemotherapy showed no reduction in mucositis.⁵²

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.⁵³ However, in a larger study, higher EGF salivary levels were associated with less severe OM.⁵⁴ A double-blind trial of EGF mouth wash 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.⁵⁵

Transforming growth factor beta 3 (TGF- β 3), which reduces epithelial cell proliferation, reduced the incidence, severity and duration of mucositis when given after chemotherapy in animal studies.⁵⁶ Clinical trials with this agent suffered from dosing concerns and results were mixed.^{57,58} Interleukin (IL)-11 demonstrated efficacy in reducing both experimental and clinical OM.⁵⁹ IL-11 was shown to modulate gene expression responsible for tumor necrosis factor alpha (TNF- α) in irradiated mucosa.⁶⁰ Similarly, benzydamine HCl has anti-TNF- α capacity. This non-steroidal anti-inflammatory agent has been shown to reduce the severity of OM during radiation therapy and to reduce oral pain.^{61,62} Benzydamine is available in many countries and is currently in phase III 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.⁶³

Glutamine has been demonstrated to have an effect upon mucosal maintenance and protection. Oral glutamine may reduce the duration and severity of radiation-induced OM⁶⁴ in patients receiving intensive

chemotherapy and HCT,^{65,66} although Okuna et al.⁶⁷ reported no alleviation of OM induced by 5-fluorouracil (5-FU) in a phase III study. A new formulation designed to increase cellular uptake of glutamine has been reported recently to result in OM prophylaxis in patients receiving chemotherapy for breast cancer.⁶⁸

A phase III study of oral chamomile mouthwash was conducted in 164 patients receiving 5-FU chemotherapy and no differences in incidence, severity, or duration of OM were seen.⁶⁹ Therefore, this mouth rinse is not recommended. There is weak evidence that allopurinol mouthwashes, which may prevent formation of oxygen-derived free radicals, can be effective in treating OM induced by 5-FU.⁷⁰

Natural honey has been reported to reduce radiation-induced OM⁷¹ and multi-center, randomized trials are warranted to validate this finding.

Infection

Systemic infection by *Candida albicans*, *krusei*, *glabrata*, and *dublinensis* species is a significant cause of morbidity and mortality in neutropenic cancer patients. Unfortunately, prevention of colonization remains elusive.⁷² Topical therapies have been shown to provide additional effect even in patients receiving systemic antifungal prophylaxis including fluconazole and amphotericin B.^{72,73} Patients must be assessed on a regular basis in order to identify clinical signs of candidal infection, especially with the increasing emergence of azole-resistant species in myelosuppressive therapy and in H&N RT. Reduced oral colonization by *Candida* species has been seen with chlorhexidine rinses.^{39,74}

Chlorhexidine has also been shown to be an effective inhibitor of oral streptococci and may impact the risk of systemic infection as well as reduce risk of dental caries due to streptococcal species.⁷⁵

Pain

Topical oral medications can reduce the need for systemic analgesics, and should be considered prior to use of systemic analgesics and continued when systemic medications are needed.

Topical anesthetics are commonly used for local oral pain but, unfortunately, most agents have only a short anesthetic effect. Agents include lidocaine, dyclonine and diphenhydramine.^{30,76} Viscous lidocaine is frequently recommended for oropharyngeal pain management, although there is a need for more studies that assess the benefits and the potential for toxicity in cancer patients.⁷⁷ Lidocaine may cause a burning

sensation, eliminate taste, affect the gag reflex, promote trauma, and may have cardiovascular and CNS effects if absorbed systemically. Dyclonine HCl may be better accepted than lidocaine.

Topical anesthetic agents have often been combined with coating agents to produce ‘magic mouthwashes’. Studies of these rinses have generally found no advantages of these combined agents over saline rinses. There is reasonable evidence to support the use of bland rinses and single topical anesthetics over these mixtures.

A single-center study indicated that a morphine mouthwash reduces the severity and the duration of OM-associated pain in patients with head and neck carcinoma.⁷⁸ Recently, formulations of topical oral transmucosal fentanyl citrate have been found tolerable in H&N RT patients with OM.⁷⁹

Doxepin rinse has been examined in a preliminary trial, with evidence of prolonged action of more than four hours of pain relief following use in cancer patients. There is no burning associated with topical use of this tricyclic antidepressant.⁸⁰ The mechanism of action of doxepin appears to be an initial anesthetic effect followed by a prolonged analgesic effect.⁸¹

Benzydamine HCl results in reduced pain and reduced use of systemic analgesics including opioids in patients with OM.^{80,82}

Oral capsaicin in a taffy-candy produced temporary pain reduction in 11 patients with OM-associated pain.⁸³ The findings suggest that the pain of mucositis is partially mediated by substance P. However, the practicality and acceptance of this approach to OM pain relief have not been demonstrated.

Dry Mouth

In patients with dry mouth, symptomatic management with mouth wetting agents is considered if salivation is not increased with systemic sialogogues. Oral pilocarpine was not found to be beneficial for radiation-induced xerostomia in a phase III placebo-controlled study.⁸⁴ The majority of agents for topical application are based on methylcellulose. Some products have incorporated fluoride, salivary enzymes, and mucins. Comparative assessments of mouth wetting agents have been conducted and can serve as a guide for choosing between commercial products.⁸⁵

Caries Prevention

Prevention of dental demineralization and caries is critical in patients with hyposalivation, as dental

breakdown can begin early following H&N RT and progress rapidly. In these patients extraction may be associated with risk of osteonecrosis, limiting treatment options.

Topical fluoride applications have been the mainstay of caries prevention following studies in the 1970s. High-concentration fluoride delivered in custom-made vinyl carriers have become the gold standard.^{86,87} In addition, other high-potency fluoride ‘brush-on’ techniques have been recommended.⁸⁸ Studies in cancer patients are needed to determine the most effective form and concentration of fluoride and means and frequency of application. In addition, studies on recently developed remineralization products remain a necessity in cancer patients.

Chlorhexidine rinse and gel have been assessed for caries risk in cancer patients.^{86,89} Chlorhexidine has the potential to control the infectious component of demineralization and caries.

Chronic Oral GVHD

Management of chronic oral GVHD includes systemic and topical immunosuppressive agents. Topical azathiopine was found to be effective in the management of painful, ulcerative oral lesions caused by GVHD.⁹⁰ When oral GVHD remains active, the topical use of cyclosporin A may represent a useful adjunctive approach.⁹¹ Recently, an effective approach has been reported using topical tacrolimus.⁹²

Conclusion

The potential for prevention and therapy, with limited risk of systemic uptake, side effects, and drug interaction, makes local delivery of various medications to mucosal tissues desirable. In addition, local administration can supplement systemic delivery of medication. The oral mucosa, gingiva, and dentition are accessible to topical therapies, but vehicles and forms of delivery of various agents need to be developed and assessed in cancer patients. Forms of delivery include topical gels or creams, rinses, lozenges, and chewing gum. Considerations in development of topical products for cancer patients include texture and viscosity of the product, taste, stability, and shelf life. Patients receiving cancer therapy require assessment of the vehicle, as oral pain, nausea, and enhanced gag reflexes may affect compliance.⁹³ Taste may change during the course of cancer therapy and taste aversions can develop. Therefore, clinical trials must be conducted in the target population. Future drug development of topical agents will enhance the ability to prevent and treat oral complications of cancer and cancer therapy. ■

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