Managing Oral Mucositis Cancer Therapy

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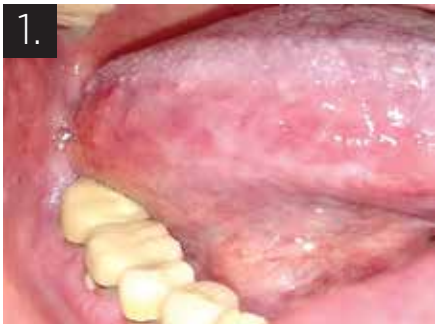
The goal of this paper is to present oral mucositis management approaches that are currently available in Canada.

It is currently estimated that over 500 Canadians will be diagnosed with cancer every day. (Canadian Cancer Society/Cancer Statistics 2014). Although advances in cancer therapy have improved survival rates for many tumor types, these treatments may cause side effects, including some in the oral cavity. One of the most debilitating effects of head and neck cancer (HNC) therapy and hematopoietic stem cell transplant (SCT) is oral mucositis, which refers to inflamed erosive/ulcerative lesions of the oral mucosa.[1-4] Oral mucositis can result from systemic chemotherapy, from radiation therapy to the oral mucosa, or a combination of these treatments. Mucositis affects between 20 percent and 40 percent of patients receiving conventional chemotherapy regimens for solid tumors, depending on the dose and cytotoxicity of the drug. In patients receiving high dose chemotherapy before a hematopoietic SCT, oral mucositis may be seen in up to 80 percent. Almost all patients receiving therapeutic radiation for head and neck cancer develop oral mucositis.[4,5] Clinical examples of erythematous and ulcerative mucositis commonly seen in head and neck cancer therapy and in bone marrow transplant are shown in Figures 1,2, and 3.

Several scales are available for measuring oral mucositis. The most commonly used scales are the World Health Organization (WHO) scale and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). Patients receiving radiation therapy to the head and neck will experience symptoms of oral mucositis within two to three weeks of radiation therapy, increasing to the end of care and resolving one to two, or more months following treatment over. In SCT patients, symptoms arise one to two weeks after chemotherapy, and may persist for weeks. The impact is significant due to associated pain, risk of infection, duration of the condition and the effect on oral and pharyngeal function. Solid tumor patients with epithelial cancers (such as breast, colon, lung) may also experience mucositis due to damage to mucosal surfaces by chemotherapy active against epithelial cells of the cancer with increased risk in later cycles of chemotherapy. In addition, new therapies (such as targeted chemotherapy) have other unique mechanisms of toxicity that may affect skin and mucosal surfaces. Common to all therapies, patients experience oropharyngeal pain and dysfunction affecting all aspects of oral function limiting oral care, use of oral prostheses, and in turn, impacting nutrition and speech. The impact of oral mucositis may lead to disruption or discontinuation of cancer therapy due to this toxicity which ultimately impacts quality of life, cost of care, and cure rates. Also, oral toxicities are linked in symptom complexes that may include fatigue, mood and cognitive change. The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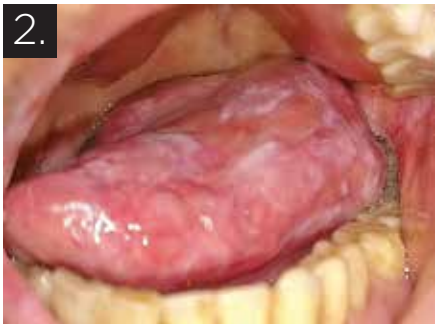
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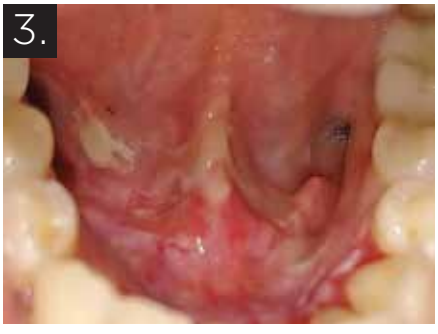
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WHO Oral Mucositis Grading Scale	
Grade	**Description**
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

Reference:
WHO: http://www.who.int/en/
WHO Handbook 1979, pp.15-22.
Sonis et al. Cancer 2004; 100(9 Suppl):1995-2025.

management of oral mucositis is aimed to prevent or reduce the severity of the toxicity and to manage the associated symptoms, which will in turn allow continuity of cancer therapy without interruption.[4,5] Management is limited by available products leading to ongoing research.

The Mucositis Study Group, of the Multinational Association for Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) has developed guidelines for mucositis in oncology, with revision in 2014.[6] These recommendations and suggestions can be viewed online (http://www.mascc.org/).

Basic oral care is the foundation of management of oral complications in cancer therapy and is strongly recommended by the Mucositis Study Group prior to, during and after cancer treatments. Basic oral care incudes dental cleaning, good oral hygiene, and oral moisturizing by regular saline/bicarbonate rinses to assist in hydrating oral tissue. Non petroleum-based lip applications, caries prevention, diet instruction (atraumatic diet), hydration and avoiding local irritants (tobacco, alcohol).

Prior to cancer treatment, a complete oral dental examination (dental radiographs, periodontal probing) and dental intervention, if indicated, should be carried out in coordination with the oncology care plan. Symptomatic dental disease should be managed along the continuum of cancer treatment, and a preventive dental program completed.

Basic oral care should be reinforced throughout cancer therapy and following treatment and when patients become symptomatic oral care should be intensified.[7] Basic oral care also includes nutritional guidance. Cancer Care Ontario has recently published a Symptom Management Guide (SMG) for Oral Care that incorporates nutritional recommendations while following the MASCC/ISOO guidelines published for management of oral mucositis. (https://www.cancercare.on.ca).

In addition to basic oral care during cancer therapy, the following therapeutic interventions have been recommended/suggested based upon well-designed studies.[6]

Cryotherapy (ice chips):

Sucking on ice chips (cryotherapy) for oral cooling has been shown *effective in reducing oral mucositis* that may be caused by intravenous cytotoxic chemotherapy that has a short half-life in the blood (such as 5-fluoruracil, high dose melphalan in SCT).

Anti-Inflammatory Agents.

Because the inflammatory response to cancer therapy is thought to play an important role in the pathogenesis of oral mucositis, several anti-inflammatory agents have been evaluated. Benzydamine (Pharixia®) is a unique non-ulcerogenic NSAID with local analgesic and anti-inflammatory properties when applied to mucosal surfaces (Fig. 4). The basis of activity appears to be via the prostaglandin pathway and activity against tumor necrosis factor that is an important effector of mucosal damage. Benzydamine is recommended as an intervention for prevention of radiation and induced oral mucositis in head and neck cancer, beginning with initiation of radiation therapy.[6,8,9] As the pivotal study provided a primary endpoint at moderate dose (5,000cGy), the MASCC/ISOO guidelines recommend receiving Benzydamine at this radiation dose based upon the design of the phase III trial. The study had few patients also receiving concomitant chemotherapy and therefore, there is not sufficient data to recommend for use in these settings. In addition to prevention of mucositis, the analgesic effects iseffects are an important additional consideration in painful mucositis. If sensitivity develops with oral rinsing, the rinse can be diluted with water (1:1, 1:2). The pivotal study was conducted in Canada and the USA, and the rinse is available in Canada (Pharixia®). ***Health Canada has***

approved Benzydamine for acute sore throat, and symptomatic relief or oropharyngeal mucositis caused by radiation therapy. The anti-inflammatory and analgesic effects may have a role to play in management of traumatic lesions and other inflammatory conditions.

Antimicrobial Agents

Several antimicrobials agent have been studied for oral mucositis based on the rationale that secondary colonization of oral mucositis ulcerations may aggravate mucosal damage. However, the results of studies testing antimicrobial agents have been mostly disappointing and are ***not recommended*** by MASCC/ISOO.[6,10] Practitioners who are not aware of the literature and the current recommendations for management of oral mucositis may inadvertently recommend these products. These agents include the rinses, such as chlorhexidine and combination products, Magic Mouth Wash, PTA lozenges or paste (polymyxin, tobramycin, amphotericin) and BCoG Lozenges and paste (bacitracin, clotrimazole, and gentamycin).[10]

> "The duration of relief is typically reported as five to 20 minutes."

Compounded Oral Rinses

Compounded products such as "magic mouthwash" are typically coating agents with variable additional ingredients; they often contain a local anesthetic, occasionally antihistamine (benedryl), antifungal, and antiseptic products in a base of milk of magnesia. Products are commonly mixed as an equal percentage of the mix for each ingredient, thereby diluting each component of the rinse, and resulting in a lower concentration of each medication in the rinse. In some cases, some constituents may interfere with the action of one of the other ingredients. The local anesthetic component may cause oral burning upon application to ulcerated surfaces, may obtund taste sensation and affect the gag reflex. Furthermore, even when effective, the duration of relief is typically reported as five to 20 minutes. As a result, these may be used before meals, but paradoxically may reduce taste sensation and mouth feel, resulting in less oral intake of food. Accordingly, these compounded rinse products are ***not*** recommended by MASCC/ISOO.[5,6] The use of chlorhexidine mouthwash was ***not*** suggested for use for the prevention or treatment of oral mucositis; however, it is noted that oral care providers may choose to use chlorhexidine for other indications unrelated to mucositis, such as oral decontamination and gingivitis.

Coating Agents

Several topical coating agents are marketed for oral mucositis, with the rationale that covering the ulcerated area will protect the nerve endings and reduce pain. Sucralfate is the most studied agent in this group; however, the lack of efficacy for sucralfate leads to recommendations ***against its use*** for prevention or treatment of oral mucositis.[10]

Low level Laser therapy

Treatment of the oral mucosa with *low-level laser therapy (LLLT) has been demonstrated to have an anti-inflammatory effect* (Fig. 5).[11,12] The MASCC/ISOO mucositis guidelines recommend the use or LLLT with a wavelength at 650nm, power of 40mW and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2 to prevent oral mucositis in patients receiving SCT. A suggestion was made for the use of LLLT in HNC (wavelength 630nm) to prevent oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy for head and neck cancer.[12]

Analgesics

Pain is the most prominent symptom or oral mucositis, and for those reasons plays a central role in the management or oral mucositis. Pain management all too often becomes the only focus of management of oral mucositis, with the important topics of oral decontamination, oral moisturization and wound healing not addressed at all.

Local delivery of analgesics has been suggested to control mucositis pain. MASCC/ISOO has suggested that compounded morphine rinses (0.2 percent) and compounded doxepin rinse (0.5 percent) may be used and were considered superior to topical local anesthetics with more profound pain effect, longer duration of action, and lack of anesthetic effect on exposed tissue.[6,10]

Management of pain commonly includes systemic analgesics with escalation of medication (from OTC to opioid) if pain increases. More recent studies suggest the potential of medications such as gabapentin for neuropathic pain also play a role in mucositis pain, as both nociceptive and neuropathic pain mechanisms are present in symptomatic mucositis.[10]

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Conclusion

Oral mucositis is a significant toxicity of systemic chemotherapy and radiotherapy to the head and neck. The morbidity or oral mucositis, includes pain, nutritional compromise, decreased quality of life, alteration in cancer tGuiherapy, risk of infection and economic costs. Guidelines and effective symptom management tools exist in the selection of effective management strategies. If mucositis can be ameliorated to decrease the costs of care driven by parenteral nutrition, opioid use, secondary infections, additional medical and hospital visits and admission to hospital, this course can have a significant positive impact on wellbeing and overall cost of care.[13-15] **OH**

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Oral Health welcomes this original article.

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