Management of Chemotherapy-Induced Oral Mucositis

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See our pullout Clinical Snapshot after page 144.

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Oral mucositis (OM) continues to be a debilitating and significant problem resulting from cytotoxic chemotherapy and head/neck radiotherapy. This inflammatory process can cause severe discomfort and functional impairment (Brown, 2010). The extent and severity of mucositis are multifactorial and involve individual patient tolerance and risk factors (Table 1) as well as specific drugs, doses, administration routes, and frequencies of chemotherapy administration (Negrin, Bedard, & Toljanic, 2010). Approximately 35% to 40% of patients receiving cytotoxic chemotherapy will develop OM (Table 2; Negrin et al., 2010). In addition to debilitation, the patient may experience severe symptoms that may lead to treatment delays or refusal of further treatment (Sonis, 2004).

Due to loss of epithelial integrity, patients with OM are at risk for bacterial and fungal infections that increase the possibility of life-threatening septicemia. Adverse consequences of uncontrolled mucositis include reduced quality of life and costly treatment measures (Lalla, Sonis, & Peterson, 2008). Therefore, control of mucositis is of paramount importance. Advanced practitioners are in an excellent position to educate patients, identify patient responses, and initiate timely treatment regimens when OM becomes an issue (Brown, 2010).

Clinical Manifestations

Mucositis is defined as the painful inflammation and ulceration of the mucous membranes lining the digestive tract. It can occur anywhere along the gastrointestinal tract (Ong et al., 2010). In particular, OM refers to the inflammation and ulceration of the mouth.

The clinical and symptomatic manifestations of OM appear as a

Table 1. Risk factors for oral mucositis

- Age: Children/older adults
- Oral health/hygiene: Preexisting dental problems, poor oral hygiene, dental caries
- Salivary secretion function: Reduced salivary flow increases susceptibility.
- Genetic factors: Higher incidence in females; patients expressing high levels of cytokines may be at higher risk.
- BMI: Low body mass (BMI < 20 for males and < 09 for females)
- Renal dysfunction: Chemotherapeutic agents may be eliminated more slowly and have a greater side-effect potential.
- Irritating substances: Use of alcohol, tobacco

Note: BMI = body mass index. Sources: Barasch & Peterson (2003); Brown (2010)

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Table 2. Cytotoxic chemotherapy agents known to cause oral mucositis

Alkylating agents	*Busulfan, carboplatin, cisplatin, *cyclophosphamide, ifosfamide, *mechlorethamine, melphalan, procarbazine, thiotepa
Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone
Antimetabolites	*Capecitabine, cytarabine, fludarabine, *5-fluorouracil, gemcitabine, hydroxyurea, 6-mercaptopurine, pemetrexed, pralatrexate
Antitumor antibiotics	Bleomycin, dactinomycin, mitomycin
Taxanes	Docetaxel (Taxotere), paclitaxel
Topoisomerase inhibitors	Etoposide, irinotecan, teniposide, topotecan

Note: *Most commonly indicated. Source: Negrin, Bedard, & Toljanic (2010).

continuum, from mild erythema to severe ulcerations with severe pain and inability to eat. Once believed to be solely a consequence of epithelial injury, mucositis is now postulated to be a biologically complex process of overlapping phases (Sonis, 2004). Mechanisms for radiation-induced and chemotherapy-induced mucositis are believed to be similar and are summarized in Table 3 (Sonis, 2004). Ongoing research is investigating cytoprotective agents, cellular nutrition, and effective mechanism-defined strategies to alter cellular response (Kurtin, 2007).

Mucositis is a self-limiting phenomenon. Symptoms due to chemotherapy typically begin 3 to 5 days after the start of therapy, peak at 7 to 10 days, and slowly subside over the next week. Continuous infusion of 5-fluorouracil, if used during radiation treatment, increases the risk of OM. Mucositis due to radiation usually appears toward the end of the second week of treatment, plateaus during the fourth week of radiation, and may persist for 2 to 3 weeks after treatment is over (Clarkson, Worthington, & Eden, 2007).

Patient Assessment

Grading systems can serve as tools for nursing assessment and provide information for intervention and treatment. Table 4 summarizes grading tools from the National Cancer Institute and the World Health Organization (WHO). Included are commonly described patient descriptions of pain levels (Nassar & Kassem, 2008).

Assessment of OM involves a multidisciplinary approach, including nurse/patient interview, physical examination, patient education, and action by the advanced practice nurse. The patient interview includes the patient's self-report of swallowing difficulty, level of discomfort, limitations of nutritional intake, and overall physical and functional changes. Oral assessment includes visual inspection focusing on such abnormal findings as color change (pallor, redness, white patches) of oral tissues, changes in mois-

Table 3. Mechanisms of radiation-induced or chemotherapy-induced mucositis

Phase	Description
Initiation of tissue injury	Chemotherapy and radiotherapy-induced damage of DNA and non-DNA targets result in the death of basal epithelial cells. Free radicals (reactive oxygen species) are generated, beginning the cascade of submucosal injury.
Message generation and upregulation	Generation of messenger signals and transcription factors and production of a variety of biologically active proinflammatory cytokines activate signals from receptors that cause cell death and tissue injury.
Signaling (amplification)	Proinflammatory cytokines accumulate and damage surrounding tissues directly. This precedes the development of overt clinical mucositis.
Ulceration	Loss of integrity of mucosa with significant inflammatory cell infiltrate. This process results in painful lesions and potential bacterial colonization.
Healing	Once causative agents are withdrawn, healing begins. Epithelial proliferation and cellular and tissue differentiation restore the integrity of the epithelium.

Note: Source: Sonis (2004)

ture (dryness, thickened saliva), changes in integrity of tissues (lesions, cracks, ulcers, bleeding), and changes in hygiene (accumulation of debris, odor). Changes in tone and quality of the voice also should be noted (Brown, 2010).

Assessment tools that may quantify mucositis are noted in the literature (Eilers & Epstein, 2004), but no standard has been established for clinical use. Advanced oncology practitioners develop an individual plan of care based on current knowledge of evidence-based treatment for oral mucositis. Implementation of interventions may be collaborative, based upon the scope of practice and clinical practice guidelines.

Management and Interventions

Strategies to minimize or prevent chemotherapy-induced mucositis have been investigated, and they continue to be at the forefront of research to improve clinical practice and outcomes in mucositis management (Clarkson et al., 2007). Frequent review and update of guidelines are important to provide comprehensive and quality care. There is currently no universal treatment strategy for managing OM. Therefore, current treatment of this condition is primarily support-

Table 4. Commonly used grading tools for oral mucositis

Tool	Grade 0	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening	Grade 5
WHO	No changes	Erythema; moist mucosa, 1–4 ulcers; no bleeding or infection; mild edema; patient avoids hot/spicy food due to oral sensitivity and experiences mild discomfort or burning sensation	Ulcers, able to eat solids; moderate erythema; > 4 lesions that are not coalescing; bleeding of mucosa with probing; mild xerostomia; moderate edema; evidence of mild infections; patient is able to drink fluids and eat soft, bland foods; moderate continual pain with use of intermittent analgesics	Ulcers; patient requires liquid diet; severe erythema; > 1 confluent ulcer; spontaneous bleeding; marked xerostomia; severe edema; infection; alimentation not possible; constant severe pain requiring systemic analgesics	Ulcers; alimentation not possible	
NCI CTC, version 4.2 (for bone marrow transplantation)	No changes	Painless ulcer or mild soreness without lesion	Painful erythema; edema or ulcers; patient can swallow	Painful erythema or ulcers preventing swallowing or requiring hydration or nutritional support	Severe ulcerations requiring prophylactic intubation or resulting in documented aspiration pneumonia	Death
NCI CTC version 4.2 (for radiation treatment)	No changes	Erythema	Patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter)	Confluent pseudo-membranous reaction ≥ 1.5 cm in diameter	Necrosis or deep ulceration	Death
NCI CTC version 4.2 (for chemotherapy)	No changes	Painless ulcers; erythema or mild soreness in the absence of lesions; asymptomatic or mild symptoms; intervention not indicated	Painful erythema, edema, or ulcers; patient can eat or swallow; moderate pain not interfering with oral intake; modified diet indicated	Painful erythema, edema, or ulcers requiring IV hydration; severe pain interfering with oral intake	Severe ulcerations or patient requires parenteral or enteral nutritional support or prophylactic intubation; life-threatening consequences; urgent intervention indicated	Death
Pain parameters	No pain	Mild pain (scored as 1–2) not requiring analgesics	Moderate pain (scored as 3–6)	Severe pain (scored as 6–9) requiring narcotics	Worst pain (scored as > 9)	

Note: NCI CTC: National Cancer Institute Common Terminology Criteria; WHO: World Health Organization Sources: National Cancer Institute (2009); Hsiao & Sonis (2010).

Table 5. Interventions for oral mucositis

Recommended for practice (strong evidence of support based on scientific data)

- Oral care
- Interdisciplinary care
- Dental prophylaxis
- Oral hygiene
- Routine oral rinses
- Hydration
- Treatment of pain

Likely to be effective

- Cryotherapy, for patients receiving bolus 5-fluorouracil or melphalan, involves swishing ice chips around the mouth for 30 minutes during administration of chemotherapy. Local vasoconstriction may result in less chemotherapy effect to the mouth.
- Palifermin, a recombinant human keratinocyte growth factor, has been shown to reduce the severity and duration of OM in patients receiving high-dose chemotherapy in the setting of HSCT.

Effectiveness not established by research (more thorough clinical trials are needed)

- Allopurinol
- Amifostine
- Anti-inflammatory rinses
- Benzydamine hydrochloride
- Flurbiprofen tooth patch
- G-CSF (subcutaneous)
- GM-CSF (subcutaneous)
- L-alanyl–L-glutamine
- Low-level laser therapy
- Multiagent (Miracle or Magic) mouthwashes
- Oral aloe vera
- Oral povidone-iodine
- Pilocarpine
- Tetracaine
- Zinc supplementation

Effectiveness unlikely (no evidence of effectiveness, although study size was small)

- Topical misoprostol
- Topical vitamin E
- Wobe-Mugos E

Not recommended for practice (ineffectiveness or harm has been clearly demonstrated; burden of cost exceeds potential benefits)

- Chlorhexidine mouthwash has demonstrated no benefit over saline rinses and might induce discomfort, taste alterations, and teeth staining.
- GM-CSF mouthwash has shown no positive effects on the severity or duration of OM.
- Sucralfate mouthwash has caused a lack of tolerance related to nausea and vomiting.

Note: G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HSCT = hematopoietic stem cell transplantation; OM = oral mucositis. Sources: Harris, Eilers, & Eaton (2009); Brown (2010). © Oncology Nursing Society, 2009; © Oncology Nursing Society, 2010.

ive and aimed at symptom control and reduction of clinical burden.

Evidence-based clinical practice guidelines for prevention and treatment of OM have been the focus of organizations that include the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (Keefe et al., 2007), Cochrane reviews (Clarkson et al., 2007), and the Oncology Nursing Society (Brown, 2010). Treatment includes pharmacologic and nonpharmacologic interventions, with recommendations categorized into five basic categories based upon the weight of evidence (Table 5; Harris, Eilers, & Eaton, 2009; Brown, 2010).

Oral Care and Clinical Practice Guidelines

It is recommended that clinics develop systematic oral care protocols that include patient, family, and staff. Recommended guidelines (Keefe et al., 2007) based upon expert opinion and limited published literature are summarized below.

An interdisciplinary approach to oral care provides the most comprehensive means of providing supportive care. Comprehensive dental prophylaxis (caries treatment; tooth extraction, if needed; cleaning) prior to chemotherapy appears to diminish the incidence of dental complications (Negrin et al., 2010).

Initial and ongoing assessment of the oral cavity is essential. Use of validated assessment tools for documentation provides opportunities for data-driven evaluation of effectiveness. Grading systems should be used as the foundation for developing an assessment tool. Institutional protocols, including consistency in use and measurement of the efficacy of interventions, will enhance the opportunities for evidence-based research results (Hsiao & Sonis, 2010).

Regular, systematic oral hygiene includes brushing with a soft-bristle toothbrush, flossing, and using nonalcohol-based rinses and moisturizers to promote healthy mucosa. The toothbrush should be allowed to dry completely before storage and replaced every 2 to 3 weeks (Brown, 2010). Adequate hydration is essential for health of the mucous membranes.

The mouth should be rinsed four or more times each day and at bedtime with a normal saline and/or sodium bicarbonate mixture. Rinses

with a bicarbonate solution, consisting of 1 tablespoon of baking soda dissolved in 1 quart of water, act as a mucolytic, helping to break up thick mucus. Rinses with saline, consisting of 1 tablespoon of table salt dissolved in 1 quart of water, act as a neutralizer. Both help to remove debris and moisturize the oral membranes. Lips can be moisturized with water-based products (Brown, 2010).

Mucosal-coating agents, such as preparations containing aluminum hydroxide, magnesium hydroxide, and simethicone (Maalox Advanced Regular) or aluminum hydroxide and magnesium hydroxide (Mylanta), may be applied locally to areas of ulceration. Compounded rinses containing an antifungal agent, an antihistamine, and topical anesthetics (Magic Mouthwash formulations), if indicated, may be used cautiously, since secondary adverse side effects (e.g., decreased gag reflex, risk of aspiration pneumonia) have been reported (Kurtin, 2007).

Assessment of oral pain with inclusion of appropriate pharmacologic intervention promotes continued nutritional intake. Topical analgesia (e.g., lidocaine preparations) may be prescribed but should be used with caution, because these agents can interfere with glottis function and put the patient at risk for aspiration. Oral nonopioid and opioid medications are prescribed based upon the patient's level of pain and relief response. The WHO's Pain Ladder is commonly used for assessment in choosing analgesia (Hsiao & Sonis, 2010).

Nutritional Recommendations

Nutritional intake can be severely compromised by pain associated with OM. Patients undergoing chemotherapy and/or radiation therapy to the head and neck may experience taste alterations. Monitoring food intake and weight is essential to assure that adequate nutrition is maintained.

Suggested strategies to improve nutritional intake may include ingestion of small, frequent meals; finely chopped meats; fruits and vegetables; milk shakes; and commercial baby foods. Patients should be instructed to avoid foods that can scrape or burn the mouth, such as potato chips, hot foods, acidic fruit, acidic juices, spicy foods, tobacco products, and alcoholic drinks. To facilitate swallowing, patients are encouraged to eat slowly, sit upright, and lean their head slightly forward (Lalla et al., 2008).

Patient Teaching Points

Involving patients in self-care and self-assessment may reduce the severity of OM. Patient education with regard to oral hygiene is stressed. Establishing a system of regular communication for patient questions and follow-up is critical. The ultimate goal of intervention is to reduce systemic infection, ensure uncompromised nutritional status, and, most importantly, maintain the patient's quality of life.

Patients should be educated and motivated to follow oral care, nutrition, and pain management guidelines to reduce the discomfort caused by OM. Education should include teaching patients to assess the oral cavity for changes. Patients should be educated to promptly report adverse findings, such as painful mouth sores that prevent eating or drinking, fever, and persistently bleeding gums (Negrin et al., 2010). Ongoing patient assessment and monitoring are needed to implement preventative and treatment strategies in a timely manner. Written instructions for home care and provision of contact information are vital for promoting confidence and peace of mind. Encouraging supportive emotional measures (e.g., support groups, counseling, or a spiritual connection) is important for many patients and families.

Summary

Mucositis presents a broad range of issues with financial, clinical, and personal consequences. Effective management of OM involves knowledge of interventions, a level of evidence supporting recommendations, and collaboration between members of a multidisciplinary team during all treatment phases. Patients may not self-report symptoms of OM due to fear of prompting an alteration in the treatment plan, such as dose reduction or delay in therapy. However, management of OM involves early self-reporting of symptoms, physical assessment, and therapy to promote the best outcomes. Written instructions, education, and verification of patient understanding help patients engage in their own treatment.

As evidence-based data continue developing in support of treatment modalities, current practices and guidelines need to reviewed and updated. Currently, minimizing symptoms through supportive measures, patient education, and sup-

portive emotional care continues to be the most effective means of managing patients with OM and optimizing their quality of life.

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