An Overview of Oral Mucositis

ABSTRACT: Mucositis, characterized by inflammation of the intestinal lining, is a debilitating consequence following treatment with radiation or certain cancer chemotherapeutic agents. A dynamic biological process, mucositis remains a bedside challenge for the health care practitioner and is a focus of laboratory research and clinical trials. Manifestations range from mild erythema to bleeding ulcerations, and patients affected by mucositis are as varied as their symptoms. Approaches aimed at preventing mucositis and therapies for ameliorating side effects are numerous. Integration of proven therapies with extensive patient education is the foundation for managing mucositis in the cancer patient.

Oral mucositis, a dose-limiting toxicity following the administration of chemotherapy or radiation, can be a debilitating experience for cancer patients. It is estimated that approximately 40% of cancer patients receiving standard-dose chemotherapy regimens will experience oral mucositis at some point during their course of treatment. The incidence is higher—approximately 75%—for patients receiving high-dose chemotherapy (such as for conditioning prior to stem cell transplantation), and the condition universally occurs in patients receiving radiation to the head and neck regions.[1-6]

Because of its substantial incidence and associated morbidity, mucositis is quite concerning for patients and health care providers. One study evaluated patients' perceptions of toxicities experienced during stem cell transplantation and found oral mucositis to be the most incapacitating patient-reported side effect. Forty-two percent of patients ranked oral mucositis as the leading cause of suffering during transplantation; this rating was significantly higher than their concern for nausea and vomiting (11%), the second most bothersome side effect.[7] Other consequences of mucositis include significant pain, difficulty with oral functional activities (e.g., chewing, swallowing, talking), delays in subsequent chemotherapy treatments, chemotherapy dose reductions, prolonged or increased hospitalizations, and increased medical costs.[2,3,8-11]

Although the terms *mucositis* and *oral mucositis* are often used interchangeably, this is not always appropriate. Since mucositis can occur anywhere along the alimentary canal, specific terminology should be used according to specific site(s) of involvement.[1,8] For the purpose of this review, *oral mucositis*, which refers to inflammation of mucous membranes lining the oropharyngeal cavity, will be referred to as *mucositis*. Additional terminology based on inflammation location can be found in **TABLE 1**.

Pathophysiology[5,8-12]

The pathophysiology of mucositis is a complex process; a precise understanding of it is evolving. Historically, mucositis was thought to develop solely as a result of chemotherapy- and/or radiation-induced damage to epithelial cells that line the mouth and throat. The rapidly dividing cells of the basal epithelium in these areas were most sensitive to the effects of radiation and/or chemotherapy. Once affected, these cells could not regenerate; thus, atrophy, ulceration, and thinning of the mucosal cells resulted. Local trauma and the presence of oral microorganisms compounded this cellular injury.[8,12]

Today, a more detailed but incomplete explanation can be offered for the exact mechanisms and processes contributing to the development of mucositis following cancer treatment. Our understanding of the pathophysiology, or more accurately, the pathobiology,[8,12] of mucositis is broader and more detailed as a result of decades of research. While mucositis is widely accepted to be a dynamic biological process that occurs on a continuum, researchers have divided the process into five stages to facilitate understanding and discussion.[5,8-12]

The first stage in the development of mucositis is *initiation*, which occurs up to two days after the administration of chemotherapy or radiotherapy. Damage to DNA contained in the cells of the basal epithelium and submucosa, in the form of strand breakage, occurs following treatment. As a result, these cells cannot properly function or replicate. Cancer therapies also generate reactive oxygen species (ROS), directly damaging cells, blood vessels, and tissues. Furthermore, the ROS act as mediators in future biological events, enhancing the development and progression of

Susannah E. Koontz, PharmD, BCOP
Clinical Practice Specialist, Pediatric Hematology/Oncology, University of Texas M.D. Anderson Cancer Center Children's Cancer Hospital, Division of Pharmacy, Houston, Texas

mucositis. At the time of initiation, the oral mucosa of patients has a normal appearance.

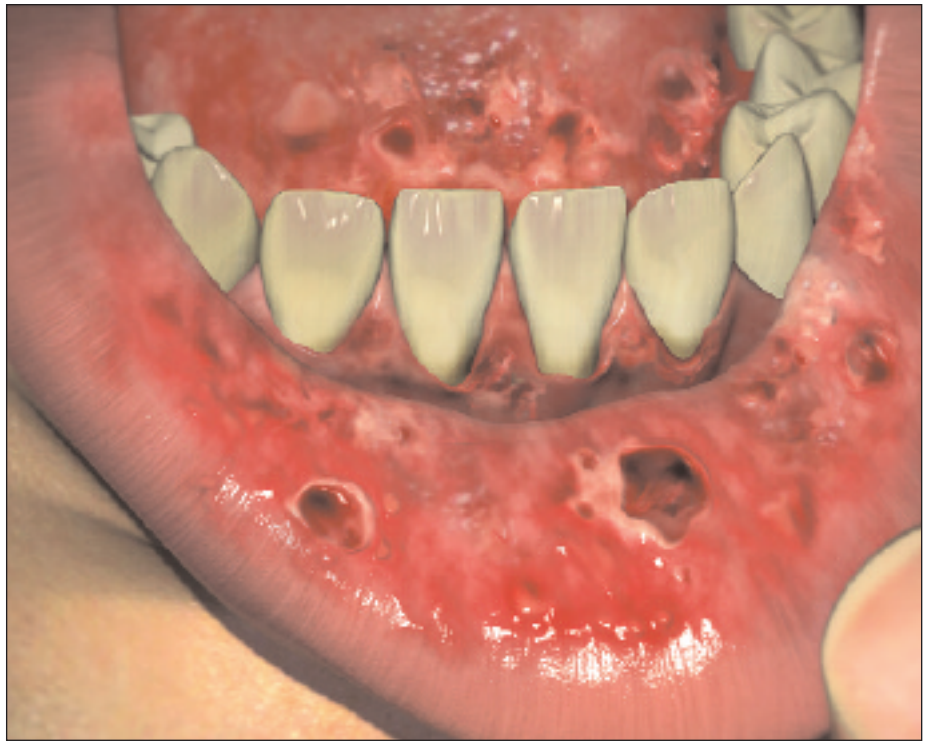
Signaling (or *primary damage response*), the second stage of mucositis, occurs two to three days after chemotherapy or radiotherapy and is characterized by several simultaneously occurring biological events. As a consequence of DNA damage, affected cells in the epithelium of the mucosa undergo apoptosis. Additionally, chemotherapy, radiation, and ROS activate transcription factors, leading to increased production of several inflammatory cytokines (e.g., tumor necrosis factor alpha [TNF-alpha], nuclear factor kappaB [NF-kappaB]). TNF-alpha production by monocytes and macrophages is increased, leading to necrosis due to changes in blood supply and regulation of immune response. During signaling, erythema and thinning of the oral mucosa is often present.

Amplification, the third stage of mucositis, occurs two to 10 days after treatment. The inflammatory cytokines produced during signaling stimulate cells in the submucosa, which in turn amplify the signals originally triggered by damage induced by chemotherapy and radiation. At this stage, NF-kappaB activation continues the cascade of inflammation and cellular damage.

Ulceration, the stage of mucositis associated with a majority of clinical signs and symptoms, occurs 10 to 15 days after chemotherapy or radiotherapy and is characterized by loss of mucosal integrity. Ulceration of oral membranes (from epithelium to submucosa) occurs, and the formation of pseudomembranes coating the ulcers can be seen. This interruption in the mucosal infrastructure facilitates the entry of bacteria, fungi, and viruses. The presence of these microorganisms, and particularly their cell wall products, activates the immune system to produce cytokines, thus compounding the degree of inflam-

Table 1. Terms Associated with Mucositis

Term	Definition
Ageusia	Inability to taste substances that are sweet, sour, salty, or bitter
Apoptosis	A form of cell death that occurs when a programmed sequence of events leads to elimination of cells without affecting other cells and tissues in the surrounding area
Arthralgia	Pain located in joints
Bacteremia	The condition of live bacteria in the bloodstream
Cytokine	Small protein released by cells affecting the behavior of cells, the interactions between cells, or the communication between cells
Dysesthesia	Altered feeling or sensation caused by neurological malfunction which can manifest as burning, wetness, electric shock, pins and needles, or itching sensation
Dysphagia	Difficulty in swallowing
Erythema	Redness of skin or mucous membranes as a result of inflammation
Esophagitis	Inflammation involving the lining of the esophagus
Hypogeusia	Decrease in the ability to taste substances that are sweet, sour, salty, or bitter
Keratinocyte growth factor	Protein that stimulates the growth of cells in tissues found in areas such as the skin and in the surface layer of the gastrointestinal tract. Regarding the gastrointestinal lining, helps maintain normal cell structure and repair damaged cells by stimulating them to divide, grow, and develop.
Macrophage	A type of white blood cell responsible for ingesting foreign material. Previous to entering tissues, macrophages were monocytes.
Monocyte	The largest cell found in normal blood and a type of white blood cell responsible for ingesting foreign material. Upon leaving blood and entering tissues, monocytes differentiate into macrophages.
Mucositis	Inflammation of mucous membranes found anywhere along the gastrointestinal tract
Neutropenia	A significant decrease in the neutrophil count that increases a patient's risk of infection
Neutrophil	A type of white blood cell responsible for digesting and killing microorganisms
Nuclear factor kappaB	Protein that helps in the regulation of cellular proliferation, immune response, inflammatory response, and apoptosis
Odynophagia	Pain associated with swallowing liquids or food
Pharyngitis	Inflammation of the pharynx; often referred to as a "sore throat"
Pruritus	Itching
Septicemia	Systemic illness as a result of virulent bacteria originating from a local seat of infection
Stomatitis	Inflammation of oral mucous membranes
Thrombocytopenia	Decrease in the number of platelets
Tumor necrosis factor alpha	Protein that possesses proinflammatory properties and can induce death of tumor cells
Xerostomia	Dryness of the mouth



Mucositis is a debilitating condition that can cause symptoms ranging from mild erythema to bleeding ulcerations and is associated with many complications.

mation and apoptosis. The risk of secondary infections, such as bacteremia and sepsis, increases, particularly in the setting of neutropenia. These painful ulcers in the oral cavity are the hallmark of this fourth stage.

Healing, the fifth and final phase of mucositis, occurs 14 to 21 days after initiation and is the restoration of mucosal integrity. Signals from the submucosal layer lead to the migration, proliferation, and differentiation of epithelial cells to ulcerative areas. Normal oral flora is restored; however, several changes at the molecular and cellular levels persist, rendering cells fragile and susceptible for future damage.

Risk Factors

Identifying patients at risk for mucositis is crucial to its prevention and treatment. Unfortunately, this task is challenging, due to interpatient variability in the incidence of mucositis. Patients with the same diagnosis and chemotherapy regimen can experience varying degrees of mucositis. Thus, clinicians believe that some inherent physiological determinants exist relating to the development of mucositis.[1,4,12] Factors recognized as increasing a patient's risk of mucositis can be divided into two groups—*patient-specific* and *treatment-related*.

Patient-specific risk factors include age, a history of smoking or tobacco use, alcohol use, preexisting oral lesions or periodontal disease, respiratory compromise, and poor nutritional status.[4,9,11,13,14] Although age is a widely recognized risk factor, the exact age-group at highest risk is still debated. Children are at higher risk for mucositis because their cells divide more rapidly and their basal epithelial cells are more sensitive to the stomatoxic effects of chemotherapy. Older patients are also at higher risk because they often experience lower healing rates related to advanced age. Additionally, this population often experiences an age-related decline in renal function, which can slow or delay their clearance of chemotherapy, thus potentiating chemotherapy toxicity.[1,4,10]

Risk factors related to the integrity of the oral mucosa are also important in mucositis development and can exacerbate its effects. Smoking, tobacco use, and alcohol use irritate the oral mucosa. Patients with periodontal disease or with poorly fitted dentures are at an increased risk of mucositis. Ill-fitting dentures not only irritate oral tissues but also serve as a reservoir for debris and increase a patient's risk of infection. Tooth decay and gingivitis can increase some of the symptoms of mucositis. Alterations in normal breathing patterns, mouth breathing, or supplemental oxygen therapy can all dry the mucosal lining of the oral cavity and increase the risk of mucositis. Finally, poor nutritional status can lend to the development of mucositis and extend its duration. High sugar intake can increase tooth decay, and inadequate caloric or protein intake can delay healing rates in patients who experience mouth ulcers.[4,5,11,14]

Therapy-related risk factors that contribute to mucositis are chemotherapy and radiation. Although any chemotherapy agent may cause mucositis, the most common offenders are listed in **TABLE 2**;[1,5,11,13,14] their propensity to produce mucositis directly correlates with their prescribed dose. Agents that affect the S phase of cellular replication (during which DNA is replicated), such as 5-fluorouracil and methotrexate, are generally more likely than other agents to cause mucositis.[14] The method of chemotherapy administration also influences the frequency of mouth sores, with continuous intravenous infusions associated with higher incidences compared to bolus administration.[5,14] Following the administration of chemotherapy, the development of mucositis usually appears approximately five to 10 days later and typically parallels the neutrophil nadir.[5,8,14]

Likewise, radiation-induced mucositis most commonly occurs during the second week of treatment.[5,8] Variable factors that influence the degree of mucositis include the volume of tissue being irradiated, the daily dose of radiation, and the cumulative dose of radiation therapy.[5,8] When radiation is combined with chemotherapy, the incidence and severity of mucositis are compounded. Radiation therapy also contributes to the development of long-term sequelae with its ability to cause permanent tissue damage, as well as physical and physiological alterations to the vasculature, glands, muscles, and bones in the head and neck region.[5,11]

Clinical Presentation and Assessment

Signs and Symptoms:[4,9,11,14] Clinical signs and symptoms usually begin to appear four to seven days following the administration of chemotherapy or radiation and are maximal seven to 14 days after cancer treatment has been initiated. The signs and symptoms of mucositis vary among patients, ranging from mild erythema to bleeding ulcerations. Ulcerations can vary in size from several millimeters to a few centimeters and may be covered in a pseudomembrane. Oral mucosa that is nonkeratinized is highly prone to the development of sores. Although any area of the mouth can become involved, the specific areas of the mouth affected to a greater degree include the ventral aspect of the tongue; the floor of the mouth; and the labial, buccal, and soft-palate mucosa.

Assessment Scales: A clinical challenge to managing mucositis is its accurate assessment. One of the first steps in recognizing mucositis is differentiating it from other clinical conditions, such as infections or trauma.[15] Once the presence of mucositis has been established, the clinician must ascertain the extent of involvement and associated symptoms. Toxicity criteria to grade the severity of mucositis are listed in TABLE 3.[16,17] Additional tools have been developed to assist the health care provider in characterizing the degree of mucositis experienced by patients. Some of these tools are often utilized for research and to assist with nursing care;[5,11,18-22] however, many assessment tools have not been validated and lack standardization among health care providers, which poses a challenge for clinical research.[23] One validated tool is the Oral Mucositis Assessment Scale. The scale, which has been documented to produce reliability among interexaminer and intraexaminer measurements, separates mucosal damage from symptomatology and oral functioning.[21]

Table 2. Chemotherapy Agents Associated with Oral Mucositis

Class of Agents	Chemotherapy Agent
Alkylating Agents	Busulfan Carboplatin Carmustine Chlorambucil* Cisplatin* Cyclophosphamide* Ifosfamide Lomustine Mechlorethamine Melphalan* Procarbazine Thiotepa
Anthracyclines	Daunorubicin* Doxorubicin* Epirubicin Idarubicin Liposomal doxorubicin
Antimetabolites	Capecitabine Cytarabine* Edatrexate* Floxuridine* Fludarabine 5-Fluorouracil* Mercaptopurine Methotrexate* Thioguanine*
Antitumor Antibiotics	Actinomycin D* Bleomycin* Mitomycin Mitoxantrone*
Taxanes	Docetaxel* Paclitaxel
Vinca Alkaloids	Vinblastine* Vincristine Vinorelbine
Other	Etoposide* Hydroxyurea Irinotecan Topotecan

** Most likely to cause oral mucositis.*

Complications from Oral Mucositis[2,3,5-7,9,11,14]

While mucositis itself is a debilitating condition, complications associated with it can be equally morbid and can significantly decrease a patient's quality of life. Pain is one of the most common symptoms of mucositis. Often, patients have difficulty chewing, dysphagia, and odynophagia secondary to pain. Compounding poor oral intake is the presence of hypogeusia or ageusia associated with mucositis. Consequential to decreased or absent oral intake, a patient's nutrition is often compromised, which can delay wound healing and recovery from other toxicities associated with cancer treatments.

As previously mentioned, patients who develop mucositis are prone to local and systemic infections. Bacterial, viral, and fungal infections are of concern in this population. Translocation of oral microorganisms can quickly lead to bacteremia or septicemia in cancer patients, especially in the context of neutropenia.

Finally, monitoring patients for long-term complications as a result of mucositis, such as xerostomia, should occur after the completion of chemotherapy or radiation. Alterations in the production of saliva, in either amount or consistency, can substantially impact a patient's qual-

ity of life, such as by affecting their ability to speak. Decreased saliva production is uncomfortable, increases a patient's risk of long-term dental complications, and can adversely affect a patient's nutritional status by impacting his or her ability to eat and swallow.

Prevention and Treatment

A variety of therapeutic modalities have been used to prevent and treat mucositis in the cancer patient. Small, uncontrolled trials have evaluated almost all of these agents, producing mixed results that may raise more questions than answers. To date, no single agent has proved effective in completely preventing mucositis. Due to the lack of concrete data regarding preventive strategies and therapeutic approaches for mucositis, consensus among health care institutions and organizations in addressing this medical problem is lacking.

In 2004, the Multinational Association for Supportive Care in Cancer (MASCC) collaborated with the International Society for Oral Oncology (ISOO) to produce clinical practice guidelines for the prevention and treatment of oral and gastrointestinal mucositis secondary to cancer-related therapy. Thirty-six panelists convened to create these evidence-based practice guidelines after review of the mucositis literature published between January 1966 and May 2002.[24] Their findings, along with updates from the panel's discussion in June 2005, are summarized in TABLE 4.[24,25] The following is an overview of some of the many therapeutic options available to prevent and treat mucositis related to chemotherapy or radiation, which are not necessarily addressed by the MASCC/ISOO guidelines. The literature contains more detailed information and additional therapies.[4,11,13-15,24,26-30]

Oral Hygiene and Diet: Judicious oral hygiene has a crucial role in preventing mucositis and attenuating its associated symptoms. All patients should be instructed on proper brushing and flossing techniques, which should be practiced routinely. A soft toothbrush should be used to help decrease gingival irritation. Alcohol-based mouthwashes should be avoided because they can irritate mouth sores and dry mucous membranes. Instead, patients should rinse with mild rinses (e.g., a solution of sodium bicarbonate) after eating and before bedtime to assist in removing debris from the mouth and maintaining a moist oropharyngeal cavity. For patients with dentures, partials, bridges, or braces, evaluation by dental staff (preferably with training in treating oncology patients) should be encouraged during high-risk periods.[4,11,14,15,24,25,27,28]

Diet has an important role in lifestyle changes for patients with mucositis. Although specific dietary plans may not prevent or treat mucositis, certain recommendations can ease difficulties associated with eating and help patients meet their daily caloric and protein needs, which can ultimately hasten recovery. In general, soft

Table 3. General Toxicity Grading Scales Used for Oral Mucositis

Scale	Clinical Setting	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)	Grade 5 (Death)
WHO	Mucositis	None	Oral soreness with or without erythema	Oral erythema, ulcers, tolerating solid diet	Oral ulcers, tolerating liquid diet only	Oral alimentation not possible	NA
NCI-CTC	Chemotherapy-induced mucositis	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful ulcers, erythema, or edema but eating or swallowing possible	Painful ulcers, erythema, or edema requiring IV hydration	Severe ulceration requiring nutritional support (enteral or parenteral) or prophylactic intubation	Death related to toxicity
NCI-CTC	Mucositis associated with HSCT	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful ulcers, erythema, or edema but swallowing possible	Painful ulcers, erythema, or edema preventing swallowing or requiring IV hydration or nutritional support (enteral or parenteral) is needed	Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia	Death related to toxicity
NCI-CTC	Radiation-induced mucositis	None	Erythema of the mucosa	Patchy, pseudomembranous reaction (patches generally <1.5 cm in greatest dimension and noncontiguous)	Pseudomembranous reaction (contiguous patches generally >1.5 cm in greatest dimension)	Deep ulceration or necrosis and occasional bleeding not induced by minor trauma or abrasion	Death related to toxicity

WHO: World Health Organization; NA: not applicable; NCI-CTC: National Cancer Institute–Common Toxicity Criteria; IV: intravenous; HSCT: hematopoietic stem cell transplantation.

foods and liquids minimize chewing and contact with mucous membranes in the oral cavity. Foods with a rough texture (e.g., tortilla chips, popcorn, granola) should be avoided to reduce the risk of local trauma. Consumption of spices, salts, and acidic foods, such as citrus fruits, should be limited or avoided, since they can irritate ulcerated areas in the mouth.[4,11,14,15,28] Additional lifestyle and dietary recommendations are listed in TABLE 5.[4,11,14,15,24,25,27,28]

Cryotherapy:[4,14,24,27,28,30,31] The use of ice chips, popsicles, or frozen beverages to prevent mucositis is considered cryotherapy. The application of cold materials into the oral cavity creates vasoconstriction, thus reducing the delivery and excretion of chemotherapy into the saliva. Having patients suck on the aforementioned items for a short time period (i.e., 30 to 60 minutes) before and during chemotherapy infusions has been shown to decrease

Table 4. Summary of MASCC/ISOO Clinical Practice Guidelines for Patients with Oral Mucositis

Area	2002 Panel Recommendations	2005 Panel Updates
Foundations of Care	Efforts to reduce the severity and duration of oral mucositis associated with radiotherapy and chemotherapy should include the use of oral care protocols, which emphasize patient education.	Oral care protocols should include both patient and staff educational components. Multidisciplinary health care teams should develop oral care protocols, and their impact should be evaluated. Protocols should include the use of a soft toothbrush that is replaced on a regular basis.
	Patient-controlled analgesia with morphine is the treatment of choice for pain relief for oral mucositis in the setting of HSCT.	No change
Prevention of Oral Mucositis Associated with Radiotherapy	None	Sucralfate is not recommended.
	None	Antimicrobial lozenges (e.g., clotrimazole troches) are not recommended.
	The use of midline radiation blocks and three-dimensional radiation treatments are recommended to reduce mucosal injury.	No change
	The use of benzydamine is recommended for head and neck cancer patients receiving moderate-dose radiation therapy.	No change
	Chlorhexidine is not recommended for use in patients with solid tumors who are receiving radiotherapy.	No change
Prevention of Oral Mucositis Associated with Standard-Dose Chemotherapy	Thirty minutes of oral cryotherapy should be administered to patients receiving 5-fluorouracil as a bolus infusion. For patients receiving bolus doses of edatrexate, 20 to 30 minutes of oral cryotherapy should used.	No change
	Acyclovir and its analogues should not be used routinely.	No change
Treatment of Oral Mucositis Associated with Standard-Dose Chemotherapy	Chlorhexidine should not be used.	No change
Prevention of Oral Mucositis Associated with Chemotherapy (+/- Total Body Irradiation) in the Setting of HSCT	None	In the setting of high-dose chemotherapy and total body irradiation with autologous HSCT for hematologic malignancies, the use of KGF-1 (palifermin) dosed at 60 mcg/kg/day for 3 days prior to chemotherapy and for 3 days post–stem cell infusion is recommended.
	None	Cryotherapy should be used in patients receiving high doses of melphalan.
	Pentoxifylline is not recommended.	No change
	Low-level laser therapy is recommended to prevent the incidence of mucositis and its associated pain for patients being treated at those centers with the technology and trained support staff.	No change

MASCC: Multinational Association for Supportive Care in Cancer; ISOO: International Society for Oral Oncology; HSCT: hematopoietic stem cell transplantation; KGF: keratinocyte growth factor.

mouth sores associated with bolus doses of 5-fluorouracil. Cryotherapy may also help prevent mucositis associated with melphalan and methotrexate. This preventive method is not feasible for prolonged infusions, due to the impracticality of having frozen items in the mouth continuously for several hours.

Mucosal Protectants, Oral Rinses, and Topical Analgesics: Agents that come into direct contact with mucous membranes in the oral cavity are *topical agents* and include mucosal protectants, oral rinses, and topical analgesics. The most widely studied topical agent is sucralfate (Carafate), a mucosal protectant most commonly prescribed as 10 mL (1 g) swished and swallowed four times daily. Sucralfate is an aluminum salt that adheres to ulcerative areas in the gastrointestinal tract, creating a protective barrier. It is also thought to increase local production of prostaglandin E_2, a mucosal protectant. Despite its extensive examination in clinical research, there remains weak evidence to support its routine use in the prevention or treatment of mouth ulcers.[4,13-15,24,27,30,32] Polyvinylpyrrolidone/sodium hyaluronate gel (Gelclair) is another mucosal protectant available for use during periods of ulceration. This concentrated gel is applied to the oral cavity one hour before eating by diluting in water and rinsing in the mouth for one minute. The barrier created improves a patient's ability to eat and drink.[4,11,24,33]

Numerous therapeutic agents, such as allopurinol, glutamine, and benzydamine, have also been used as oral rinses to combat mucositis. As a topical mouthwash, allopurinol (concentration of 1 to 16 mg/mL) has demonstrated inconsistent benefit to warrant its routine use.[13,14,29,30] Formulated as an oral suspension, the abundant amino acid glutamine, or more specifically L-glutamine, has demonstrated some clinical benefit by reducing the severity and duration of mucositis caused by chemotherapy. Since some of the clinical research examining glutamine's effectiveness has received criticism, its precise utility is unclear, and further study is suggested.[11,13,14,24,27,30] Alternatively, benzydamine, a nonsteroidal analgesic with anesthetic, anti-inflammatory, and antimicrobial properties, has been proved to reduce the incidence of radiation-induced mucositis when administered as a 0.15% oral rinse. The MASCC/ISOO guidelines have recognized the role of benzydamine; however, it is not commercially available in the United States.[13,14,24,27]

Multiagent rinses lack data demonstrating efficacy in preventing or treating mucositis.[4,24,28] Referred to as *magic mouthwashes*, these mixtures are individually formulated from one institution to another to contain such ingredients as chlorhexidine, diphenhydramine, nystatin, viscous lidocaine, and antacid suspensions.[4,11,27,28] Chlorhexidine, in particular, is frequently avoided in patients experiencing mucositis, as it can be irritating and is associated with a bad taste and staining of the teeth.[4,11,14,24] The analgesic capsaicin has produced some favorable data in a pilot study. When applied to oral membranes, capsaicin was found to increase patients' pain thresholds. Its benefits are thought to derive from the ability to promote reepithelialization of damaged areas in the mouth.[4,14,34]

Systemic Therapies: During clinical investigations examining the use of colony-stimulating factors such as filgrastim and sargramostim to decrease the incidence and severity of chemotherapy-induced neutropenia, patients with mucositis were positively impacted. Patients experienced milder clinical symptoms and brevity in their course of mucositis. Unfortunately, investigations using colony-stimulating factors to prevent mucositis in patients receiving chemotherapy regimens known to produce only mild neutropenia have not been favorable.[14,24,27]

Palifermin (Kepivance), a recombinant human keratinocyte growth factor (KGF), is a promising systemic

Table 5. Patient Information*

Lifestyle Recommendations

- Use mouth care regimens as directed.
- Avoid tobacco use and alcohol consumption.
- Use water-based moisturizers to protect lips.
- Chew sugar-free gum, suck on sugar-free candy or ice chips, or sip water to alleviate decreased saliva production or dry mouth. Patients may also want to consult their doctor about a saliva substitute.
- Brush the teeth, tongue, gums, cheeks, and palate well using a soft toothbrush at least twice a day, preferably after meals.
- Use a foam toothbrush or swab as directed if a soft toothbrush cannot be tolerated.
- Change the toothbrush or swab often, as directed by a physician.
- Use a regular-flavored fluoride toothpaste without tartar control or peroxide.
- Floss at least once a day using waxed dental floss.
- Use a bland mouth rinse after brushing or flossing.
- Avoid alcohol-based mouth rinses.
- Ensure dentures are properly fitted.
- Clean dentures as directed every time oral care is performed.
- See a dentist regularly as directed by a physician.

Dietary Recommendations

- Avoid foods that are rough in texture or salty, spicy, or acidic.
- Avoid foods at extreme temperatures.
- Incorporate soft foods into the diet.
- Maintain adequate fluid intake.
- Avoid carbonated beverages.
- Use a straw to ingest liquids.
- Cook foods until tender and consider blending or pureeing foods for easier consumption.
- Use melted butter or margarine, sauces, creams, and gravies to moisten food.
- Cut food into small pieces and chew well before swallowing.
- Try to maintain a high-protein/high-calorie diet to aid in healing of mouth sores.

** Recommendations apply before, during, and after treatment.*

agent shown to significantly impact mucositis in patients. It specifically targets epithelial cells, binding to KGF receptors to stimulate cellular proliferation, differentiation, and migration, and ultimately facilitating the epithelial cell repair process. Approved in January 2005, palifermin is indicated for decreasing the incidence and severity of oral mucositis associated with high-dose chemotherapy in the context of hematopoietic stem cell support for treatment of hematological malignancies. Based on a pivotal phase III trial, palifermin, when compared to placebo, not only impacted mucositis by decreasing the degree and duration of symptoms but also improved patients' ability to maintain daily functions and decreased the need for total parenteral nutrition and opioid use.[35,36] Due to its promising utility in decreasing the incidence and severity of mucositis in the transplant setting, the MASCC/ISOO updated guidelines endorse its use.[25] Current investigations examining palifermin's role in other clinical contexts, such as in head and neck cancer, are ongoing.

Adjunctive Therapies: Supportive care of patients with mucositis is as important as treating the condition. Patients often experience some degree of pain during an episode. Pain that is not relieved by topical analgesics or oral narcotics warrants the use of systemic narcotics—preferably, morphine sulfate delivered through patient-controlled analgesia.[11,24] Nutritional difficulties and deficiencies should also be addressed. If changes to lifestyle and dietary alterations do not allow for adequate intake of protein and caloric needs, initiation of enteral or parenteral nutrition is frequently considered.[11] Administration of appropriate antibiotic, antifungal, and/or antiviral therapy to treat identified pathogens is crucial in patients with documented infections.[11,15,37,38] Finally, patients should routinely receive education regarding mucositis and its treatment.

Summary

The management of mucositis remains a clinical dilemma. Although a paucity of data exists that examines the utility of various therapeutic approaches, definitive options to entirely prevent or completely treat mucositis in the cancer patient are lacking. Future research in this area will continue to contribute more to our understanding of the biological process, thus increasing the potential in identifying promising therapeutic targets. Until more is known about mucositis, current valid treatment modalities coupled with patient education is the best option for caring for patients with mucositis. ■

REFERENCES

1. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 Suppl):1995-2025.
2. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer*. 2003;98:1531-1539.
3. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol*. 2001;19:2201-2205.
4. Eilers J. Nursing interventions and supportive care for the prevention and treatment of oral mucositis associated with cancer treatment. *Oncol Nurs Forum*. 2004;31(4 Suppl):13-23.
5. Dodd M. The pathogenesis and characterization of oral mucositis associated with cancer therapy. *Oncol Nurs Forum*. 2004;31(4 Suppl):5-11.
6. Peterson DE. Oral problems in supportive care: no longer an orphan topic? *Support Care Cancer*. 2000;8:347-348.
7. Bellm LA, Epstein JB, Rose-Ped A, et al. Patient reports of complications of bone marrow transplantation. *Support Care Cancer*. 2000;8:33-39.
8. Sonis ST. A biological approach to mucositis. *J Support Oncol*. 2004;2:21-32.
9. Sonis ST. Oral mucositis in cancer therapy. *J Support Oncol*. 2004;2(6 Suppl 3):3-8.
10. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol*. 1998;34:39-43.
11. Cawley MM, Benson LM. Current trends in managing oral mucositis. *Clin J Oncol Nurs*. 2005;9:584-592.
12. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4:277-284.
13. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1, pathogenesis and prophylaxis of mucositis. *Head Neck*. 2003;25:1057-1070.
14. Kostler WJ, Hejna M, Wenzel C, Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. *CA Cancer J Clin*. 2001;51:290-315.
15. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 2, diagnosis and management of mucositis. *Head Neck*. 2004;26:77-84.
16. World Health Organization. *Handbook for Reporting Results of Cancer Treatment*. Geneva, Switzerland: World Health Organization; 1979.
17. National Cancer Institute. Cancer Therapy Evaluation Program (CTEP): Common Toxicity Criteria (CTC) Version 2.0. Available at: ctep.cancer.gov/reporting/ctc_archive.html. Accessed February 17, 2006.
18. Beck S. Impact of a systematic oral care protocol on stomatitis after chemotherapy. *Cancer Nurs*. 1979;2:185-199.
19. Eilers J, Berger AM, Petersen MC. Development, testing, and application of the oral assessment guide. *Oncol Nurs Forum*. 1988;15:325-330.
20. Schubert MM, Williams BE, Lloid ME, et al. Clinical assessment scale for the rating of oral mucosal changes associated with bone marrow transplantation: development of an oral mucositis index. *Cancer*. 1992;69:2469-2477.
21. Sonis ST, Eilers JP, Epstein JB, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer*. 1999;85:2103-2013.
22. McGuire DB, Peterson DE, Muller S, et al. The 20 item oral mucositis index: reliability and validity in bone marrow and stem cell transplant patients. *Cancer Invest*. 2002;20:893-903.
23. Stokman MA, Sonis ST, Dijkstra PU, et al. Assessment of oral mucositis in clinical trials: impact of training on evaluators in a multi-centre trial. *Eur J Cancer*. 2005;41:1735-1738.
24. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer*. 2004;100(9 Suppl):2026-2046.
25. Mucositis Study Group for the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (2005). Mucositis: perspectives and clinical practice guidelines – updated June 2005. Available at: www.mascc.org/index.php?load=pro_study_groups&page_id=73. Accessed February 17, 2006.
26. Worthington HV, Clarkson JE, Eden OB. Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev*. 2004:(2):CD001973.
27. Plevova P. Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review. *Oral Oncol*. 1999;35:453-470.
28. Wohlschlaeger A. Prevention and treatment of mucositis: a guide for nurses. *J Pediatr Oncol Nurs*. 2004;21:281-287.
29. Stone R, Fliedner MC, Smiet AC. Management of oral mucositis in patients with cancer. *Eur J Oncol Nurs*. 2005;9(Suppl 1):S24-S32.
30. Naidu MU, Ramana GV, Rani PU, et al. Chemotherapy-induced and/or radiation therapy-induced oral mucositis—complicating the treatment of cancer. *Neoplasia*. 2004;6:423-431.
31. Mahood DJ, Dose AM, Loprinzi CL, et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. *J Clin Oncol*. 1991;9:449-452.
32. Loprinzi CL, Ghosh C, Camoriano J, et al. Phase III controlled evaluation of sucralfate to alleviate stomatitis in patients receiving fluorouracil-based chemotherapy. *J Clin Oncol*. 1997;15:1239-1243.
33. Innocenti M, Moscatelli G, Lopez S. Efficacy of Gelclair in reducing pain in palliative care patients with oral lesions: preliminary findings from an open pilot study. *J Pain Symptom Manage*. 2002;24:456-457.
34. Berger A, Henderson M, Nadoolman W, et al. Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. *J Pain Symptom Manage*. 1995;10:243-248.
35. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004;351:2590-2598.
36. Kepivance (palifermin) package insert. Thousand Oaks, Calif: Amgen; 2005.
37. Heimdahl A. Prevention and management of oral infections in cancer patients. *Support Care Cancer*. 1999;7:224-228.
38. Herrstedt J. Prevention and management of mucositis in patients with cancer. *Int J Antimicrob Agents*. 2000;16:161-163.