Presented at the 2006 Chicago Supportive Oncology Conference, Chicago, Illinois

Diagnosis and Management of Oral Mucositis

Sol Silverman, Jr., MA, DDS

Abstract Oral mucositis is a common complication in cancer patients receiving chemotherapy and/or radiation therapy. Nearly all patients undergoing myeloablative therapy for stem-cell or bone marrow transplantation experience oral mucositis. Those receiving radiation therapy for head and neck cancer are at especially high risk. However, this toxicity also occurs with standard-dose chemotherapy and can be seen in association with treatment of many other tumor types. Oral mucositis significantly complicates cancer treatment by contributing to pain, dysphagia, weight loss, depression, higher risk of infection, decreased quality of life, and increased healthcare costs. This review summarizes the impact of oral mucositis in patients with cancer, including its pathogenesis, diagnosis, financial implications, and management. Current treatment guidelines are presented, and novel targeted therapies are discussed. Newer agents, such as palifermin (recombinant human keratinocyte growth factor-1), have been shown in clinical trials to reduce the incidence and severity of oral mucositis, and Saforis (an oral glutamine suspension) may also promote recovery from mucosal damage following chemotherapy or radiation therapy. Continued advances in understanding the pathobiology of oral mucositis should lead to the development of additional agents for its effective prevention and treatment in patients undergoing cancer therapy.

Patients receiving chemotherapy and/or radiation therapy often develop oral mucositis, which can significantly complicate cancer treatment. Mucositis can cause pain and dysphagia, resulting in depression in some patients. These problems are further complicated by the associated xerostomia and alterations in taste that can lead to anorexia, weight loss, and weakness. Severe inflammation and injury to the oral mucosa can also increase the likelihood of oral or systemic infections.[1] Taken together, these complications can significantly complicate treatment, extend hospitalization, decrease patient quality of life, and increase costs.

Given that hundreds of thousands of patients worldwide are affected by mucositis annually,[1] a significant need for effective therapy exists. Various palliative treatments have been evaluated for prophylaxis and treatment but have not proven uniformly effective, and more effective approaches are needed. This review summarizes the causes and impact of oral mucositis in cancer therapy and discusses emerging treatments that may prevent its occurrence and ameliorate the severity of associated symptoms.

Incidence

Mucositis is a common adverse event among patients receiving chemotherapy and/or radiation therapy, particularly in those treated with myeloablative therapy for stem-cell transplantation (SCT; Table 1).[2] In general, the risk of oral mucositis increases as a function of the type of cancer therapy used, with the lowest risk occurring with "gentler" chemotherapeutics such as gemcitabine (Gemzar) and the higher risk occurring with more aggressive agents such as 5-fluorouracil (5-FU) and cisplatin and/or radiation therapy.[3]

Dr. Silverman is Professor of Oral Medicine, University of California San Francisco School of Dentistry, San Francisco, California.

Oral mucositis and xerostomia frequently occur in patients with squamous cell carcinoma of the head and neck (SCCHN) who are treated with radiation therapy directed at the oral and pharyngeal regions.[2,4] Trotti and colleagues[2] studied more than 6,000 patients with SCCHN who received radiotherapy with or without chemotherapy. The overall incidence of mucositis in this patient population was 80%, with 39% of cases being grade 3/4, which limited or prevented alimentation. Patients who received altered fractionation radiotherapy (RT-AF) were particularly at risk; all patients in this subgroup experienced mucositis, with 57% scored as grade 3/4. In patients who received only chemotherapy, the incidence of mucositis was 22%.

Between 50% and 100% of patients undergoing SCT experience mucositis as a result of high-dose chemotherapy or total-body irradiation (TBI).[5] In SCT patients, Sonis and colleagues[6]

Correspondence to: Sol Silverman, Jr., MA, DDS, UCSF School of Dentistry, 513 Parnassus Avenue, San Francisco, CA 94143; telephone: (415) 476-2045; fax: (415) 476-4204; e-mail: silvermans@dentistry.ucsf.edu

J Support Oncol 2007;5(suppl 1):013–021

Table 1

Incidence of Oral Mucositis Among Cancer Patients

	INCIDENCE (%)	GRADE 3/4 (%)
Radiotherapy for head and neck cancer	85–100	25–45
Stem-cell transplantation	75–100	25–60
Solid tumors with myelosuppression	5–40	5–15

Adapted from Trotti et al[2]

Diagnosis and Management of Oral Mucositis

found that a higher oral mucositis rating correlated with an increased risk of significant infection, an increased number of days in the hospital, a greater use of opioids and total parenteral nutrition (TPN), higher healthcare costs, and an elevated 100-day mortality rate. Other studies suggest that the severity of mucositis may be higher with allogeneic transplants than with autologous transplants.[6,7]

A smaller but still significant proportion of patients who receive standard-dose chemotherapy also develop mucositis as a result of therapy. A retrospective analysis[8] of oral and gastrointestinal (GI) mucositis in nearly 600 patients receiving myelosuppressive chemotherapy revealed that mucositis developed during 37% of 1,236 cycles of chemotherapy. Episodes of bleeding were significantly more common during cycles with GI mucositis than during those without GI mucositis (13% vs 8%; $P = 0.04$), as were episodes of infection (73% vs 36%; $P < 0.0001$). After adjustments for other predictive factors, oral mucositis was found to be significantly correlated with infection (odds ratio [OR], 2.4; $P < 0.0001$), whereas GI mucositis was associated with both bleeding (OR, 2.0; $P = 0.01$) and infection (OR, 2.24; $P < 0.0001$). Of note, these authors projected that in patients with grade 3/4 mucositis and myelosuppression, an estimated 74.5% will develop infection, and 9.1% will die.[8] The risk of grade 3/4 oral or GI mucositis is significantly higher in patients with solid tumors treated with standard-dose chemotherapy who are myelosuppressed compared with all patients. Severe mucositis has been noted in association with the treatment of many types of solid tumor, although the risk of grade 3/4 toxicity appears higher for patients with genitourinary cancer, lung cancer, and sarcoma.[8]

The clinical impact of oral mucositis was clearly evident in an analysis of patients with solid tumors who developed chemotherapy-induced myelosuppression.[8] Compared with patients who did not develop oral mucositis, those who did had higher rates of infection and antibiotic use (68% vs 36%), more weight loss (61% vs 54%), increased use of antiviral therapy (45% vs 10%) and antifungal drugs (34% vs 6%), and more frequent chemotherapy dose reductions (25% vs 11%) and delayed cycles (11% vs 9%).

Economic Impact

Mucositis and its treatment can have a significant economic impact. Patients incur increased costs for treatment, including in some cases hospitalization or emergency room visits for complications or life-threatening situations. In the previous retrospective analysis of patients who received myelosuppressive therapy with or without radiation therapy, the average cost for treating patients without oral mucositis was $3,893. In contrast, this figure nearly doubled to $6,618 in patients with grade 1/2 oral mucositis and rose to $9,458 in those who developed grade 3/4 toxicity.[8] The overall incidence of mucositis-related hospitalization was 16% in three studies involving a total of 700 patients; the rate was highest in patients receiving RT-AF (32%).[2]

In a study of 92 patients undergoing SCT, severe GI mucositis associated with myelosuppressive or myeloablative therapy was found to lengthen hospitalization by an average of 2.6 days, increase the time on TPN and use of opioids, and add $25,405 to the mean hospitalization cost compared with those without mucositis.[6] Total hospitalization costs increased as a function of severity of oral mucositis, as did the 100-day mortality rate.

Similarly, Elting and colleagues[8] found that the mean length of hospitalization was 4 days, 6 days, and 12 days during cycles with no mucositis, oral mucositis, and GI mucositis, respectively. As previously noted, oral mucositis may result in increased use of antibiotics and can cause dose reductions and/or delays in chemotherapy or radiotherapy. These results demonstrate that oral mucositis—particularly severe mucositis—is associated with increased healthcare utilization, significantly greater hospitalization and treatment costs, and higher mortality. Consequently, therapy designed to prevent its occurrence or accelerate its resolution should result in significant clinical benefit as well as healthcare cost savings.

Pathogenesis

Recent advances in understanding the pathobiology of oral mucositis suggest a complex, mul-

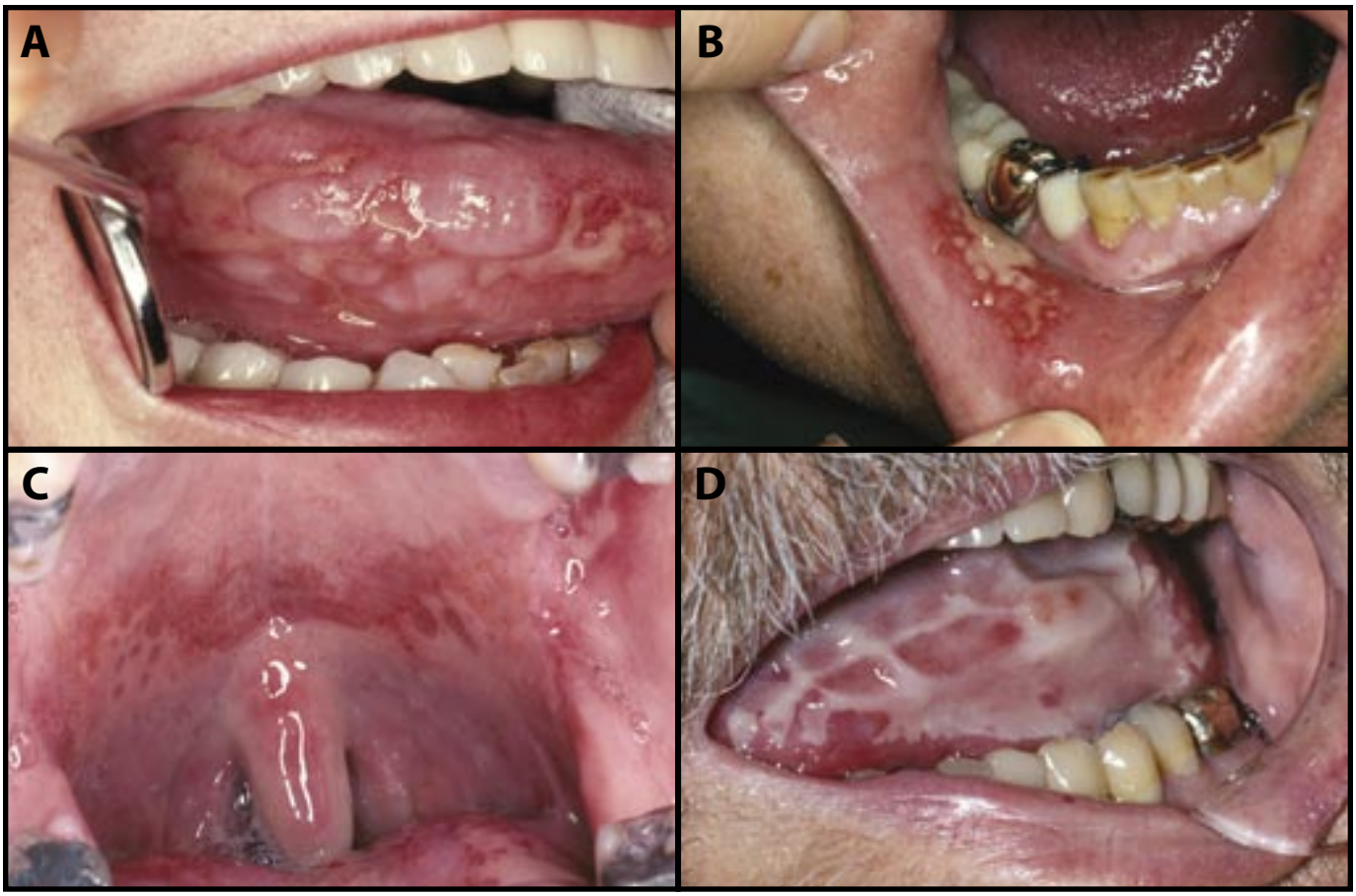

Figure 1 Clinical Appearance of Oral Mucositis in Patients With Cancer

(A) Oral mucositis following radiation therapy. **(B)** In another patient, note mucosal lesions induced by radiation effects on an adjacent gold crown. **(C and D)** Neutropenic-associated grade 4 mucositis following myelosuppressive therapy in two patients. Inflammation and ulceration can be seen on the oropharynx in the left panel **(C)**, and severe mucositis affecting the tongue is apparent on the right panel **(D)**.

tistep process. Sonis[9] has proposed a model to characterize the major steps in its development and resolution. In the initiation phase, reactive oxygen species (ROS) generated by exposure to chemotherapy or radiation therapy result in DNA strand breaks and damage to cells, tissues, and blood vessels, which ultimately cause apoptosis. Such damage triggers activation of transcription factors such as nuclear factor kappa B (NF-κB), which in turn causes signaling and amplification through gene upregulation. Increasing levels of cytokines like interleukin (IL)-1β and IL-6 trigger the initiation of various pathways that damage epithelial cells and surrounding fibroblasts. Proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), further increase the activity of NF-κB, causing a feedback loop that promotes the cycle of inflammation, pain, and functional impairment. Penetration of the epithelium into the submucosa can occur in the ulceration phase, allowing colonization by oral bacteria and increasing the risk of sepsis. It is likely that each of these stages of mucositis pathogenesis occurs in a continuous, overlapping manner. Since each cycle of chemotherapy or radiation therapy is thought to trigger this cascade of events, this series of dynamic interactions likely occurs at different oral mucosa sites repeatedly during the course of cancer therapy.[9]

These models of the pathogenesis of oral mucositis have suggested a variety of potential therapeutic targets, which have resulted in the development of agents that can prevent or ameliorate associated symptoms (see section on "Targeted Therapies"). Several such compounds are thought to inhibit one or more

Table 2

Updated Guidelines for Management of Oral Mucositis

CLINICAL PRACTICE	RECOMMENDATIONS
Pain management	• Regular oral pain assessment using validated self-assessment instruments • Topical anesthetics, other agents as needed
Oral assessment and oral care	• Regular assessment using validated instruments • Preventive and therapeutic oral care regimens • Routine, systematic oral hygiene • Interdisciplinary approach to oral care
Dental care	• Dental evaluation and treatment prior to initiating anticancer therapy (hygiene, teeth, periodontal) • Inclusion of dental professionals as an integral part of the interdisciplinary healthcare team
General	• Education of staff, patients, and families to ensure adherence to good oral care • Outcome assessment to improve quality of care

Based on guidelines issued by the Basic Oral Care Group of the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO)

Adapted from McGuire et al[17]

Diagnosis and Management of Oral Mucositis

steps in these pathways, thus enhancing their effectiveness. Since some agents act to down-regulate NF-κB activation, which is involved in upregulating numerous genes encoding proinflammatory cytokines, the resulting inhibition may be greatly enhanced.

Diagnosis

Oral mucositis is typically diagnosed based on the clinical appearance, location, timing of oral lesions, and use of certain types of therapy known to be associated with mucositis. For example, stomatotoxic chemotherapeutics generally result in lesions on the unkeratinized movable mucosa, with less frequent involvement of the keratinized hard palate, dorsal surface of the tongue, or gingiva.[10] Radiation therapy can also induce mucositis in a similar fashion. Representative examples of the appearance of oral mucositis are shown in Figure 1.

Other common conditions can have a similar clinical presentation to oral mucositis and may confuse the differential diagnosis. They include oral candidiasis (thrush), herpes simplex virus (HSV), and graft-versus-host disease (GVHD) in transplant patients (Figure 2). Candidal overgrowth (candidiasis), which occurs in response to radiation therapy and/or chemotherapy, usually responds well to systemic antifungal medication. HSV is frequently seen in immunocompromised cancer patients receiving chemotherapy,[11] with lesions appearing on the lips (cold sores) or intraoral mucosa.[12] Initiation of antiviral therapy may ameliorate HSV-associated stomatitis and reduce symptoms. Oral mucositis can also occur in patients receiving myeloablative conditioning regimens for allogeneic hematopoietic SCT and in those with GVHD, affecting the oral mucosa and gingiva.[13] Consequently, accurate diagnosis of oral mucositis is critical to ensure selection and timely initiation of optimal therapy.

Several scoring systems have been devised to assess the severity of oral mucositis and its treatment, but no one scale is uniformly employed. The two most common scales are those proposed by the World Health Organization (WHO) and the National Cancer Institute Common Toxicity Criteria (NCI–CTC).[10] Low grades (1 and 2) indicate a condition that allows dietary intake, whereas the more severe grades (3 and 4) limit or completely preclude the intake of solid food. In addition, Sonis et al[14] have devised an Oral Mucositis Assessment Scale (OMAS), which is more quantitative for clinical research but may be difficult to use in routine clinical care. Other scoring systems have been proposed,[15] but the lack of standardization has hampered their acceptance.

Treatment

TREATMENT GUIDELINES

Treatment guidelines for oral mucositis were issued in 2004[16] and recently were updated by the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO).[17] Guidelines issued by the Basic Oral Care Group subcommittee reviewed 32 relevant studies published in the literature between 2000 and 2005. Discussions by the panel resulted in the development of a set of recommendations on the prevention and treatment of oral mucositis (Table 2).

These guidelines emphasize basic oral care, an interdisciplinary approach to oral care, routine assessment of oral care and pain management using validated instruments, and regular dental assessment and dental care prior to the start of cancer therapy. Any irritants to the oral mucosa (eg, spicy foods or alcohol) should be avoided. The panel stressed the need for education of staff as well as patients and their families on proper oral care and the importance of outcome assessment using quality-improvement processes.

Currently, there is insufficient high-level

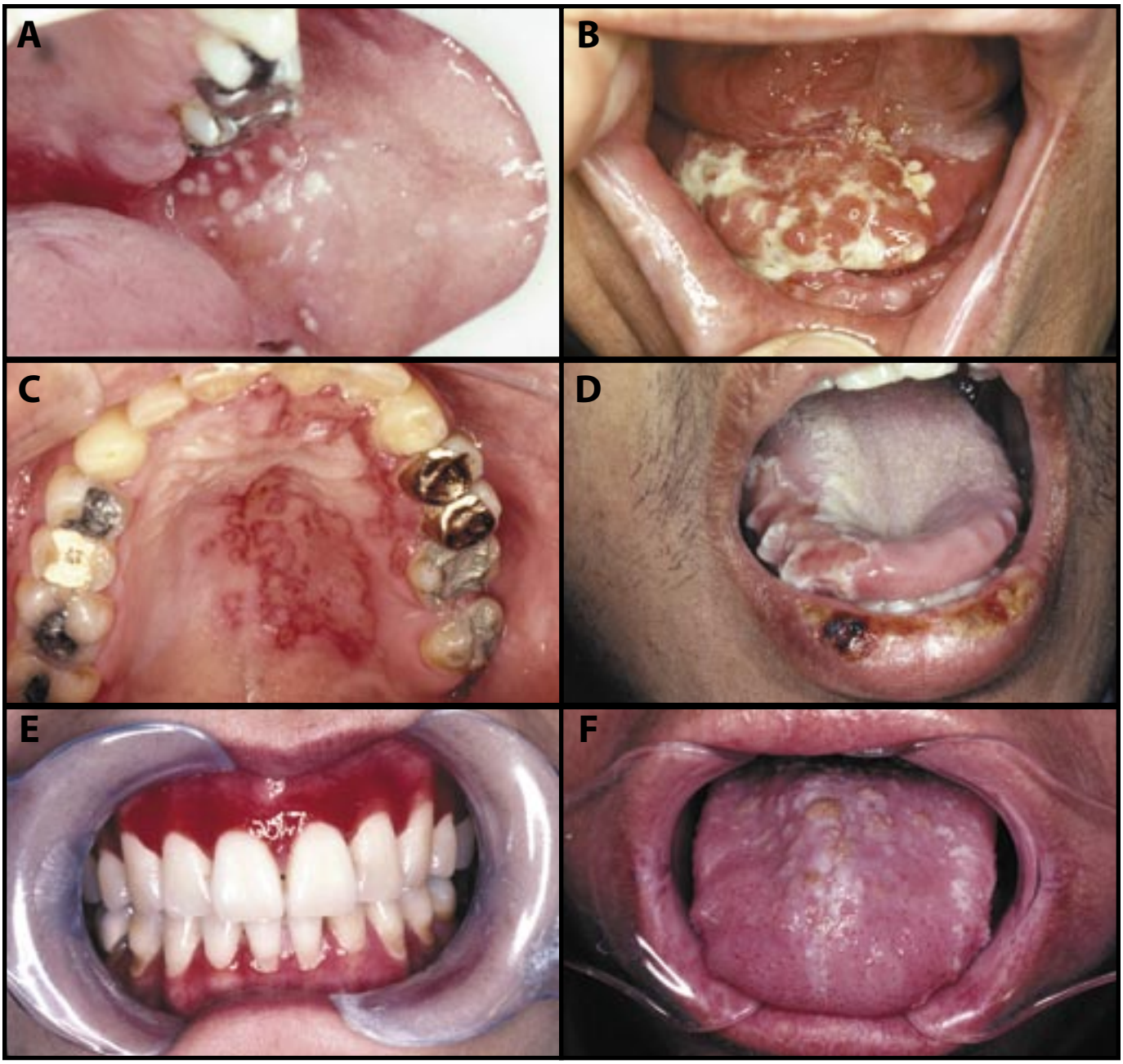

Figure 2 Differential Diagnosis of Oral Mucositis

Oral mucositis can resemble **(A and B)** candidiasis (thrush), herpes simplex virus (HSV) on the palate **(C)** and oral-labial HSV in another immunosuppressed patient **(D)**, and **(E and F)** graft-versus-host disease in two patients.

evidence to recommend the use of bland and/or medicated oral rinses for treatment of oral mucositis, although they may help to reduce the degree of gingivitis and plaque as well as the risk of caries. Mucositis-related pain should be carefully managed through the use of topical analgesics and nonsteroidal agents and patient-controlled analgesia (opioids) for severe pain when necessary.

PREVENTION OF RADIATION-INDUCED ORAL MUCOSITIS

For patients receiving radiation therapy, use of mid-line radiation blocks and conformal radio-

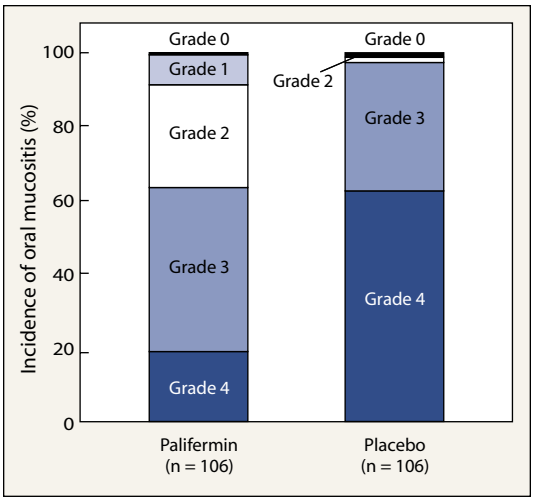

Figure 3 Effect of Palifermin on the Incidence and Severity of Oral Mucositis

Patients with hematologic cancers undergoing intensive chemotherapy and radiotherapy in conjunction with stem-cell transplantation were treated with palifermin or placebo. Palifermin-treated patients had a lower incidence of grade 3/4 oral mucositis than did those who received placebo ($P < 0.001$).

therapy (CRT) may help to prevent the occurrence of oral mucositis. Shielding of normal tissues with mid-line mucosa-sparing blocks may minimize acute radiation-induced toxicity.[18,19] In patients with advanced head and neck cancer, careful control of the radiation dose and volume using three-dimensional (3D) CRT has not compromised tumor control but has decreased toxicity compared with standard radiotherapy.[20] Similarly, high-dose rate intraoperative radiation therapy (IORT) allows delivery of radiation directly to the tumor bed and thus may minimize radiation exposure to normal tissues and may reduce toxicities such as oral mucositis.[21] However, at the site of implantation, there is an increased risk for mucositis.

A meta-analysis of randomized clinical trials of interventions designed to prevent oral mucositis induced by radiotherapy and/or chemotherapy was recently performed.[22] A total of 45 studies involving 8 different therapies were evaluated. Only four interventions demonstrated some protective effect on the development or severity of oral mucositis: PTA (polymyxin E, tobramycin, and amphotericin B), with an OR of 0.61, granulocyte-macrophage colony-stimulating factor (GM-CSF; OR, 0.53), oral cooling (OR, 0.3), and amifostine (Ethyol; OR, 0.37). Additional approaches are clearly needed for more effective prevention and therapy.

TARGETED THERAPIES

A number of targeted therapies have recently been evaluated for prevention and/or treatment of oral mucositis, including amifostine and other antioxidants, growth factors, cytokines, and glutamine.

Amifostine. Amifostine is a radioprotectant that has been widely studied for prevention of oral mucositis induced by chemotherapy or radiation therapy. This agent is believed to act as a free radical scavenger, protecting against ROS generated by exposure to radiation.[23] Amifostine has been approved in the United States for reducing the incidence of severe xerostomia in patients with head and neck cancer associated with radiation therapy but has not been approved for oral mucositis. It has also been shown to protect against mucositis induced by treatment with epirubicin and gemcitabine[24] and to reduce the incidence of severe (grade 3/4) oral mucositis in patients treated with chemoradiotherapy for head and neck cancer.[25]

Investigators of a randomized phase III trial[26] of 303 patients with previously untreated head and neck cancer who received radiation therapy found that amifostine reduced the incidence of ≥ grade 2 acute xerostomia but had no effect on mucositis. Additionally, a recent meta-analysis[27] of 1,451 cancer patients who received radiation therapy with amifostine demonstrated a statistically significant reduction in the risk of mucositis (OR, 0.37; 95% confidence interval [CI], 0.29–0.48; $P < 0.00001$). However, adverse effects associated with amifostine, such as nausea, vomiting, hypotension, and allergic reactions, are significant and can limit its clinical utility.

Other Antioxidants. Given the encouraging activity seen with amifostine, other compounds that can inhibit ROS have been evaluated for protection against oral mucositis. Benzydamine hydrochloride can inhibit the production of inflammatory cytokines and may thus reduce mucosal damage due to radiation. Topical application of the antioxidant *N*-acetylcysteine (NAC) was found to reduce the severity of oral mucositis in animal models.[28] Use of an oral rinse containing benzydamine hydrochloride decreased the incidence of oral mucositis in a randomized, placebo-controlled trial[29] of patients with head and neck carcinoma who received radiation therapy. Benzydamine hydrochloride also delayed use of analgesics when compared with pla-

cebo. This agent has not yet been approved for use in the United States.

Growth Factors. In some studies, use of hematopoietic colony-stimulating factors has resulted in a reduction in oral mucositis associated with cancer therapy. Kannan and colleagues[30] found that GM-CSF protected against radiation-associated mucositis in a study of 10 patients with head and neck cancer, but this effect was not seen in other studies.[31] In a randomized trial, subcutaneous injection of GM-CSF in 29 patients undergoing radiotherapy for early-stage laryngeal cancer resulted in a decrease in the severity of mucositis,[32] and similar results were observed in patients who were irradiated for oral and oropharyngeal tumors.[33] However, use of a mouthwash containing GM-CSF was not effective as prophylaxis for oral mucositis in cancer patients undergoing high-dose chemotherapy with autologous SCT.[34]

Studies have indicated that granulocyte colony-stimulating factor (G-CSF) has generally shown less activity than GM-CSF in this regard. In eight lymphoma patients who received high-dose methotrexate, G-CSF–based mouthwash decreased the severity of oral mucositis compared with placebo.[35] Yet another small study of patients receiving hyperfractionated radiation therapy saw no decrease in mucositis with use of G-CSF, although there were fewer treatment breaks.[36] Larger randomized trials of these agents are needed to establish their efficacy in chemotherapy- or radiation therapy-induced oral mucositis.

Cytokines. The pleiotropic cytokine IL-11 has been investigated to mitigate the mucotoxic effects of radiation therapy and chemotherapy and has demonstrated activity in small animal models.[14] In a phase II study,[37] IL-11 was administered to patients who received high-dose conditioning regimens and allogeneic SCT for hematologic malignancies. However, determination of the benefit of IL-11 was not possible due to the high mortality rate on this trial. Edema and cardiac arrhythmia are potential side effects of IL-11 therapy.[38]

Palifermin. Palifermin (Kepivance), or recombinant human keratinocyte growth factor-1, is another compound shown to reduce oral mucositis induced by radiation therapy and cytotoxic chemotherapy. Palifermin has multiple mechanisms of action, including downregulation of proinflammatory cytokines; inhibition of epithelial cell DNA damage and apoptosis; and stimulation of epithelial cell growth, differentiation, and migration.[39] In murine models, palifermin treatment prior to chemoradiotherapy exerted a protective and trophic effect on the intestinal mucosa and salivary glands.[40]

Clinical trials have demonstrated that palifermin can exert a mucoprotective effect in patients who were treated with chemotherapy or radiation therapy. A small study of 64 patients with metastatic colorectal cancer who received 5-FU/leucovorin demonstrated a lower incidence of oral mucositis (grade 2 or higher) and less severe symptoms than did controls when palifermin was administered for 3 days prior to chemotherapy.[41]

In a study of 212 patients with hematologic cancers who received intensive chemoradiotherapy in conjunction with SCT, palifermin (60 μg/kg/d) was given for 3 consecutive days prior to the initiation of conditioning therapy and after autologous SCT.[42,43] Although palifermin significantly decreased the incidence of grade 3/4 oral mucositis (63% vs 98%; $P < 0.001$), the reduction in grade 4 oral mucositis was even more impressive (20% vs 62%; $P < 0.001$; Figure 3). Significant reductions were also achieved in the incidence of mouth and throat soreness, use of opioid analgesics, and use of TPN. Moreover, decreased healthcare costs and improved quality of life were noted in this study. Palifermin-related adverse effects included skin toxicities (rash, erythema, edema, and pruritus), oral toxicities (dysesthesia, tongue discoloration, tongue thickening, dysgeusia), and arthralgia.[44] Ongoing trials are further evaluating the ability of palifermin to reduce oral mucositis in patients receiving chemoradiotherapy for head and neck cancer and in the transplant setting.

Glutamine. Many malignancies are characterized by decreased glutamine levels, which can be further exacerbated by cell damage caused by cancer therapy. Glutamine supplementation can reverse this effect and may help to protect mucosal tissues from damage by radiation therapy or chemotherapy and thus accelerate recovery.[45] Saforis (AES-14; glutamine combined with UpTec, an advance drug delivery system) was developed as a swish-and-swallow treatment for patients receiving chemotherapy or radiation therapy.

An early trial of oral glutamine suspension was conducted in 21 women with metastatic breast cancer treated with high-dose paclitaxel and melphalan (Alkeran) as a conditioning regimen for autologous SCT.[46] Patients who used glutamine experienced a decrease in the severity and dura-

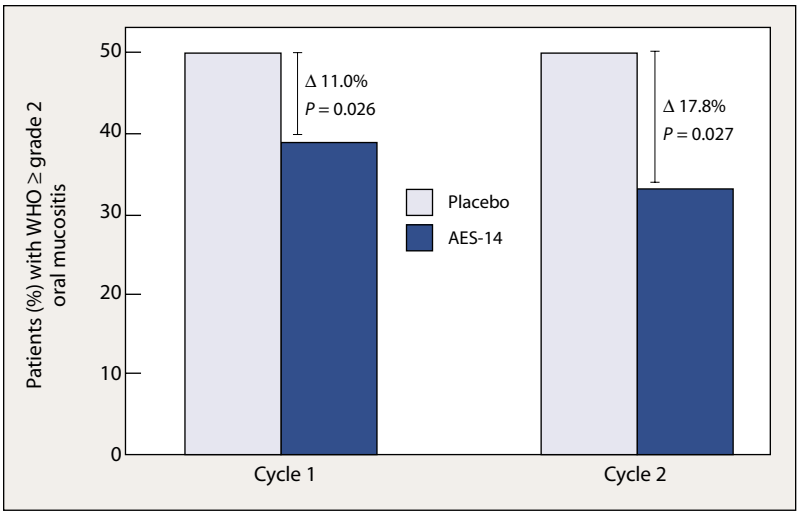

Figure 4 Carryover Effect of Saforis in Phase III Trial of Patients With Breast Cancer Treated With Chemotherapy

The 326 women who developed oral mucositis (grade ≥ 2) due to chemotherapy were randomized to receive treatment with Saforis (2.5 g three times daily) or placebo for 14 days. Saforis significantly reduced the incidence of oral mucositis compared with placebo in cycle 1. Patients who crossed over from Saforis to placebo in cycle 2 experienced a further reduction in the risk of mucositis compared, suggesting a carryover effect.

Adapted from Peterson et al[47]

Diagnosis and Management of Oral Mucositis

tion of oral mucositis, with less need for parenteral morphine for pain relief.

These results led to a placebo-controlled, crossover phase III trial that evaluated the ability of Saforis to reduce the incidence and severity of oral mucositis in breast cancer patients receiving chemotherapy.[47] Of 2,084 patients treated with multiple cycles of 5-FU, doxorubicin, and cyclophosphamide, oral mucositis (WHO grade ≥ 2) developed in 326 women. This subset of patients was randomized to treatment with Saforis (2.5 g three times daily) or placebo for 14 days following chemotherapy.

Saforis reduced the incidence of oral mucositis (grade ≥ 2) by 22% compared with placebo ($P = 0.026$) as well as the duration ($P = 0.048$). In patients who crossed over from Saforis to the placebo arm in cycle 2, there was a suggestion of a carryover effect, with a 36% reduction in the risk of mucositis compared with placebo alone ($P = 0.027$; Figure 4). There was no increase in the incidence of adverse effects related to Saforis treatment. These data suggest that this agent may be useful in preventing or reducing the incidence and severity of oral mucositis in patients undergoing cancer therapy.

Conclusion

Mucositis is a clinically important toxicity that is often encountered with cytotoxic chemotherapy or radiation therapy. Ulceration of the oral mucosa can impair patients' ability to swallow and eat and may inhibit appetite, lengthen hospitalization and use of antibiotics, and increase the risk of infection from bacteremia. Moreover, healthcare costs associated with oral mucositis and its treatment can be substantial. Prompt, accurate diagnosis of oral mucositis by oncologists and initiation of prophylaxis and therapy are therefore essential.

Although several preventive and therapeutic approaches have been evaluated, no single agent has been found to be superior. In some trials, free radical scavengers, such as amifostine and NAC, have reduced the severity of symptoms, but these agents have not yet been approved for treatment of oral mucositis in the United States. More recently, elucidation of the pathogenesis of mucositis and the cellular pathways underlying its development has suggested potential therapeutic targets. Significant reductions in the incidence and severity of oral mucositis have been observed in clinical trials of palifermin and the oral glutamine suspension Saforis. Continued evaluation of these compounds, as single agents and in combination regimens, is ongoing, and they should improve treatment outcomes.

References

PubMed ID in brackets

1. Duncan M, Grant G. Oral and intestinal mucositis—causes and possible treatments. Aliment Pharmacol Ther 2003;18:853–874. [14616150]

2. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66:253–262. [12742264]

3. Peterson DE. New strategies for management of oral mucositis in cancer patients. J Support Oncol 2006;4(suppl 1):9–13. [16499139]

4. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. Cancer 2006;107:2525–2534. [17078052]

5. Bellm LA, Epstein JB, Rose-Ped A, et al. Patient reports of complications of bone marrow transplantation. Support Care Cancer 2000;8:33–39. [10650895]

6. 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. [11304772]

7. Rapoport AP, Miller Watelet LF, Linder T, et al. Analysis of factors that correlate with mucositis in recipients of autologous and allogeneic stem-cell transplants. J Clin Oncol 1999;17:2446–2453. [10561308]

8. 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. [14508842]

9. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer 2004;4:277–284. [15057287]

10. Scully C, Sonis S, Diz PD. Oral mucositis. Oral Dis 2006;12:229–241. [16700732]

11. Tang IT, Shepp DH. Herpes simplex virus infection in cancer patients: prevention and treatment. Oncology (Williston Park) 1992;6:101–106, 109. [1322152]

12. Khan SA, Wingard JR. Infection and mucosal injury in cancer treatment. J Natl Cancer Inst Monogr 2001;29:31–36. [11694563]

13. Cutler C, Li S, Kim HT, et al. Mucositis after allogeneic hematopoietic stem cell transplantation: a cohort study of methotrexate- and non-methotrexate-containing graft-versus-host disease prophylaxis regimens. Biol Blood Marrow Transplant 2005;11:383–388. [15846292]

14. 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;85:2103–2113. [10326686]

15. Sonis ST, Elting LS, Keefe D, et al; Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004;100(9 suppl):1995–2025. [15108222]

16. Rubenstein EB, Peterson DE, Schubert M, et al; Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(suppl):2026–2046. [15108223]

17. McGuire DB, Correa ME, Johnson J, Wienandts P. The role of basic oral care and good clinical practice principles in the management of oral mucositis. Support Care Cancer 2006;14:541–547. [16775649]

18. Ship JA, Eisbruch A, D'Hondt E, Jones RE. Parotid sparing study in head and neck cancer patients receiving bilateral radiation therapy: one-year results. J Dent Res 1997;76:807–813. [9109831]

19. Perch SJ, Machtay M, Markiewicz DA, Kligerman MM. Decreased acute toxicity by using midline mucosa-sparing blocks during radiation therapy for carcinoma of the oral cavity, oropharynx, and nasopharynx. Radiology 1995;197:863–866. [7480771]

20. Mantini G, Manfrida S, Cellini F, et al. Impact of dose and volume on radiation-induced mucositis. Rays 2005;30:137–144. [16294906]

21. Hu K, Ship JA, Harrison LB. Rationale for integrating high-dose rate intraoperative radiation (HDR-IORT) and postoperative external beam radiation with subcutaneous amifostine for the management of stage III/IV head and neck cancer. Semin Oncol 2003;30(suppl 18):40–48. [14727239]

22. Stokman MA, Spijkervet FKL, Boezen HM, et al. Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. J Dent Res 2006;85:690–700. [16861284]

23. Grdina DJ, Kataoka Y, Murley JS. Amifostine: mechanisms of action underlying cytoprotection and chemoprevention. Drug Metab Drug Interact 2000;16:237–279. [11201306]

24. Stokman MA, Wachters FM, Koopmans P, et al. Outcome of local application of amifostine (WR-1065) on epirubicin-induced oral mucositis: a phase II study. Anticancer Res 2004;24:3263–3267. [15510621]

25. Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;52:739–747. [11849797]

26. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000;18:3339–3345. [11013273]

27. Sasse AD, Clark LG, Sasse EC, Clark OA. Amifostine reduces side effects and improves complete response rate during radiotherapy: results of a meta-analysis. Int J Radiat Oncol Biol Phys 2006;64:784–791. [16198504]

28. Blonder J, Etter J, Samaniegoet A, et al. Topical bioadhesive antioxidants reduce the severity of experimental radiation induced oral mucositis. Proc Am Soc Clin Oncol 2001;20:1606.

29. Epstein JB, Silverman S Jr, Paggiarino DA, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled trial. Cancer 2001;92:875–885. [11550161]

30. Kannan V, Bapsy PP, Anantha N, et al. Efficacy and safety of granulocyte macrophage-colony stimulating factor (GM-CSF) on the frequency and severity of radiation mucositis in patients with head and neck carcinoma. Int J Radiat Oncol Biol Phys 1997;37:1005–1010. [9169806]

31. Tejedor M, Valerdi JJ, Arias F, et al. Hyperfractionated radiotherapy concomitant with cisplatin and granulocyte colony-stimulating factor (filgrastim) for laryngeal carcinoma. Cytokines Cell Mol Ther 2000;6:35–39. [10976537]

32. McAleese JJ, Bishop KM, A'Hern R, Henk JM. Randomized phase II study of GM-CSF to reduce mucositis caused by accelerated radiotherapy of laryngeal cancer. Br J Radiol 2006;79:608–613. [16823067]

33. Masucci G, Broman P, Kelly C, et al. Therapeutic efficacy by recombinant human granulocyte/monocyte-colony stimulating factor on mucositis occurring in patients with oral and oropharynx tumors treated with curative radiotherapy: a multicenter open randomized phase III study. Med Oncol 2005;22:247–256. [16110136]

34. Dazzi C, Cariello A, Giovanis P, et al. Prophylaxis with GM-CSF mouthwashes does not reduce frequency and duration of severe oral mucositis in patients with solid tumors undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue: a double blind, randomized, placebo-controlled study. Ann Oncol 2003;14:559–563. [12649101]

35. Karthaus M, Rosenthal C, Huebner G, et al. Effect of topical oral G-CSF on oral mucositis: a randomised placebo-controlled trial. Bone Marrow Transplant 1998;22:781–785. [9827976]

36. Mascarin M, Franchin G, Minatel E, et al. The effect of granulocyte colony-stimulating factor on oral mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy. Oral Oncol 1999;35:203–208. [10435157]

37. Antin JH, Lee SJ, Neuberg D, et al. A phase I/II double-blind, placebo-controlled study of recombinant human interleukin-11 for mucositis and acute GVHD prevention in allogeneic stem cell transplantation. Bone Marrow Transplant 2002;29:373–377. [11919725]

38. Smith JW 2nd. Tolerability and side-effect profile of rhIL-11. Oncology (Williston Park) 2000;14(suppl 8):41–47. [11033837]

39. Blijlevens N, Sonis S. Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis. Ann Oncol 2006; advance access published on October 9, 2006; doi:10.1093/annonc/mdl332. [17030544]

40. Borges L, Rex KL, Chen JN, et al. A protective role for keratinocyte growth factor in a murine model of chemotherapy and radiotherapy-induced mucositis. Int J Radiat Oncol Biol Phys 2006;66:254–262. [16904525]

41. Rosen LS, Abdi E, Davis ID, et al. Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. J Clin Oncol 2006:24:5194–5200. [17075109]

42. 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. [15602019]

43. Stiff PJ, Emmanouilides C, Bensinger WI, et al. Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. J Clin Oncol 2006;24:5186–5193. [16391299]

44. Siddiqui MA, Wellington K. Palifermin: in myelotoxic therapy-induced oral mucositis. Drugs 2005;65:2139–2146. [16225371]

45. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev 2003;29:501–513. [14585260]

46. Cockerham MB, Weinberger BB, Lerchie SB. Oral glutamine for the prevention of oral mucositis associated with high-dose paclitaxel and melphalan for autologous bone marrow transplantation. Ann Pharmacother 2000;34:300–303. [10917373]

47. Peterson DE, Jones JB, Petit RG. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. Cancer 2007;109:322–331. [17154160]