

# Managing mucositis in head and neck cancer patients undergoing radiation therapy

Suzanne McGettigan, MSN, CRNP, AOCN®,  
and Carrie Tompkins Stricker, MSN, CRNP, AOCN®

University of Pennsylvania Health System, Philadelphia, PA

Oral mucositis is a common complication of cancer treatments and is often the dose-limiting toxicity in treating head and neck cancers. This condition affects patients' quality of life, increases the risk for systemic infection, and impairs nutrition. In addition to the type of malignancy and antineoplastic therapy, a patient's risk factors for the development of oral mucositis include baseline oral health, immune status, and decreased salivary production. Standardized grading scales should be used to assess oral mucositis on all patients at risk. To prevent the development of oral mucositis, good oral hygiene should be encouraged in all patients undergoing radiation therapy to the head and neck. Oral hygiene remains the basis of care when treating oral mucositis. Single-agent topical analgesics can be used for symptomatic relief and systemic analgesia should be used when appropriate. Currently, many additional therapies are under investigation for use in the prevention and treatment of oral mucositis including palifermin, velaferrin, granulocyte-macrophage colony-stimulating factor, L-glutamine, and many other cytokines.

**O**ral mucositis is a common complication of cancer treatments such as chemotherapy and radiotherapy. It is characterized by erythema, inflammation, pain, and ulceration and can occur in up to 100% of patients undergoing stem cell transplantation, radiotherapy to the head and neck, and stomatotoxic chemotherapy.<sup>1,2</sup> Usually, oral mucositis is a dose-limiting toxicity when treating head and neck cancers. In one large (n = 450) retrospective review of stage III or IV head and neck cancer patients undergoing radiation therapy, 83% developed mucositis.<sup>3</sup> Significantly more patients with mucositis (59%) required unplanned delays/breaks in therapy than did those without mucositis (16%).

Patients undergoing conventional radiation therapy to the head and neck typically experience erythema and mouth soreness within 2 weeks of beginning therapy and often develop more severe damage to the epithelium within an additional 2 weeks.<sup>4</sup> When chemotherapy and radiotherapy are administered concurrently, the incidence and sever-

## KEY POINTS

A common complication of cancer therapies, oral mucositis is a dose-limiting toxicity during treatment of head and neck cancer.

Patients undergoing treatment for head and neck cancer should be assessed on a regular basis with an established grading scale.

Basic oral care should be initiated in all patients undergoing radiotherapy to the head and neck.

Ongoing efforts focus on improving methods to prevent and treat oral mucositis in head and neck cancer patients.

Manuscript received August 31, 2006; accepted October 2, 2006.

Correspondence to: Suzanne McGettigan, MSN, CRNP, AOCN®, Oncology Nurse Practitioner, Department of Medicine, University of Pennsylvania Health System, 16 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104; telephone: 215-662-6397; fax: 215-662-2432; e-mail: McGettis@uphs.upenn.edu.

Commun Oncol 2006;3:653-656 © 2006 Elsevier Inc. All rights reserved.

Overview of WHO oral toxicity scale

Grade	Subjective and objective assessments of oral mucosa
Grade 0	Normal, moist tissue
Grade 1	Erythema present or absent Soreness No ulceration
Grade 2	Erythema present or absent Ulceration Ability to tolerate solid foods
Grade 3	Erythema present or absent Ulceration Inability to tolerate solid foods
Grade 4	Erythema present or absent Ulceration Inability to tolerate oral intake

ity of oral mucositis are even greater, often leading to delays in treatment and reduction in therapeutic dose.<sup>3</sup>

Mucositis significantly affects patients' quality of life, interfering with daily activities such as talking and eating, increasing the risk for systemic infections and possibly hospitalization, and impairing general nutrition.<sup>5</sup> In one study of individuals undergoing stem cell transplant, those who experienced mucosal ulceration required 5.8 additional days of narcotics and had 2 additional febrile days compared with those without mucositis.<sup>6</sup> In a separate study of solid tumor patients undergoing chemotherapy, those experiencing mucositis had approximately twice as many infections as those who did not have mucositis.<sup>7</sup>

**Pathophysiology**

The development of mucositis is now thought to be multistep process involving an initiation/vascular phase, an epithelial phase, a signaling/up-

regulation phase, an ulcerative phase, and a healing phase.<sup>6,8,9</sup>

■ During the inflammatory or vascular phase, the insult of chemotherapy or radiotherapy generates reactive oxygen species within epithelial cells, which release multiple cytokines, resulting in inflammation.

■ During the epithelial phase, multiple cytokines and transcription factors are up-regulated, leading to apoptosis and tissue damage.

■ During the ulcerative phase, severe ulceration provides an environment for the invasion of bacteria and other microorganisms. This leads to an increase in the concentration of macrophages and induces a second peak in cytokine production.

■ During the healing phase, cell proliferation and differentiation allow restoration of the epithelium, although repair at the cellular level continues.<sup>4,6,8</sup>

In patients receiving radiation therapy to the head and neck region, permanent complications include physical damage to the salivary glands.

**Assessment**

The development of oral mucositis is predominantly influenced by the type of malignancy and the cytotoxic therapy administered, but patient factors also play a role, including poor oral health at baseline, existing mucosal damage, impaired immune status, and decreased salivary production.<sup>9,10</sup> Other factors proposed but not consistently supported in clinical studies include patient age (children and older adults are at greater risk), female gender, low body mass, smoking, and poor nutritional status.<sup>11</sup>

Many grading scales are available for describing oral mucositis. The most commonly used in clinical trials are the World Health Organization Oral Toxicity Scale and the National Cancer Institute Common Toxicity Criteria scale.<sup>8</sup> The more detailed Oral Assessment Guide developed by Eilers et al<sup>12</sup> has been incorporated as an assessment tool in mucositis clinical practice

guidelines.<sup>13</sup> These and other tools for assessing oral mucositis are discussed in detail in a recent review on measurement of oral mucositis.<sup>11</sup> Regardless of the scale used, a systematic and routine assessment of the oral cavity should be performed in all patients deemed to be at risk for developing oral mucositis. In addition to the objective, physical manifestations of mucositis (such as ulceration, dryness, and erythema), there are functional and subjective manifestations of mucositis, including pain and an impaired ability to eat and/or to participate in daily activities. Any patient who will receive radiotherapy to the head and neck region should have a thorough assessment of the oral cavity before initiation of therapy and at regular intervals during treatment.

The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) published clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis in 2004,<sup>2</sup> which were updated in 2005.<sup>14</sup> Sections of the MASCC/ISOO guidelines that are relevant to the care of patients with head and neck cancer are discussed here.

Individuals who develop oral mucositis, should be assessed for infection with HSV-1 (herpes simplex virus-1), since nearly 50% of head and neck cancer patients with ulcerative mucositis had HSV infection on smear in one small randomized trial.<sup>15</sup> Treatment with antivirals was associated with reduced severity of mucositis in these patients.

**Prevention**

*Basic oral care*

Although the evidence supporting the efficacy of basic oral care in preventing mucositis is weak,<sup>16</sup> it is accepted that good basic oral care improves mucosal health, integrity, and function.<sup>2</sup> MASCC/ISOO consider a basic oral care protocol to be a core

NCI Common Toxicity Criteria (v2): oral mucositis in radiation therapy

Grade	Appearance of oral mucosa
Grade 0	Normal oral mucosa
Grade 1	Erythema
Grade 2	Patchy pseudomembranous reaction
Grade 3	Confluent pseudomembranous reaction
Grade 4	Necrosis or deep ulceration

component of oral mucositis prevention and management strategies, including the use of a soft toothbrush that is replaced on a regular basis. The guidelines panel also advocates the use of oral care protocols developed by a multidisciplinary team as well as patient and staff education aimed at reducing the severity of mucositis. Other recommended components of good oral hygiene, which have been incorporated into published oral care protocols,<sup>13</sup> include flossing, rinsing with bland oral rinses, and using mouth moisturizers.<sup>17</sup> Foam swabs are not as effective as toothbrushes in reducing plaque and preventing caries.<sup>17</sup>

#### Topical oral agents

A number of topical oral agents have been investigated for their ability to prevent or reduce the severity of cancer treatment-induced mucositis.

Topical antibiotic lozenges may have some mild benefit in preventing mucositis, but evidence is limited.<sup>16</sup> Sucralfate has consistently been shown to offer no improvement over placebo in preventing the incidence of mucositis or relieving associated pain.<sup>16</sup> Chlorhexidine, an antimicrobial mouth rinse, has failed to significantly reduce the incidence, severity, and time to resolution of mucositis.<sup>16</sup> MASCC/ISOO recommends against using any of those three agents to prevent radiation-induced oral mucositis and recommends against using chlorhexidine to treat established oral mucositis in patients receiving chemotherapy.<sup>14</sup> Hydrogen peroxide can actually break down granulation tissue and impede recovery from mucositis.

The MASCC/ISOO panel recommends benzydamine oral rinse, an anti-inflammatory agent, for prophylaxis against mucositis in head and neck cancer patients undergoing radiotherapy,<sup>14</sup> based on results from a multicenter randomized trial in that population.<sup>18</sup> However, it was not effective in patients receiving accelerated radiotherapy doses ( 220 cGy/d), and a more recent mul-

ticenter randomized trial showed no advantage of benzydamine use among patients receiving head and neck radiotherapy.<sup>19</sup> Benzydamine is not approved for use in the United States.

#### Other agents

Amifostine (Ethyol) is a free radical scavenger that has been evaluated for its efficacy in preventing radiation-induced mucositis in patients with head and neck cancer.<sup>16</sup> A recent Cochrane review concluded that it appears to provide a small benefit in terms of preventing mucositis and reducing its severity,<sup>16</sup> but a recent randomized trial was unable to confirm such a benefit.<sup>20</sup> MASCC/ISOO guidelines recommend using amifostine only to reduce the incidence of esophagitis in non-small cell lung cancer patients undergoing combination chemotherapy and radiotherapy. In randomized trials, amifostine is associated with a greater incidence of vomiting compared with placebo.<sup>17</sup>

#### Nonpharmacologic strategies

For patients receiving radiotherapy to the head and neck region, the MASCC/ISOO panel recommends midline radiation blocks and three-dimensional radiation treatment. Other strategies, ranging from simple oral cryotherapy to the technologically complex low-level laser therapy, have been evaluated in specific populations but are not relevant to individuals with head and neck cancer. The MASCC/ISOO guidelines discuss these strategies in detail.<sup>2,14</sup>

#### Treatment

Good oral hygiene remains the cornerstone of care for these patients, given that it reduces the impact of oral bacterial flora and helps limit opportunistic infection.<sup>16</sup> The few interventions of established efficacy for patients who develop oral mucositis include the following:

- Oral rinses should be used with regular frequency, and no rinse appears

to be more effective and well tolerated than normal saline solution.<sup>13</sup>

- Single-agent topical analgesics can be used for symptomatic relief and include lidocaine, Ulcerase, and Gelclair. Compounded mouth rinses should be avoided.<sup>13</sup>

- Systemic analgesics, including patient-controlled analgesia, should be implemented as needed to reduce the pain associated with severe mucositis.<sup>2</sup>

#### Future directions

- Palifermin, a recombinant keratinocyte growth factor, is being studied in clinical trials of patients undergoing combined chemoradiotherapy for locally advanced head and neck cancers.<sup>21</sup> Theoretically, it could protect or stimulate replication of epithelially derived malignant cells<sup>21</sup>; therefore, disease-free and overall survival are included as clinical endpoints in these trials.<sup>22</sup>

- Velafermin is a recombinant human fibroblast growth factor protein being studied in autologous stem cell transplant patients.<sup>23</sup>

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates production of granulocytes, macrophages, and dendritic cells and regulates their function in the dermis and submucosa. Small studies examining subcutaneously administered GM-CSF in

#### Resources

**From CancerCare, a downloadable patient guide to mucositis:**

[http://cancer.org/pdf/booklets/ccc\\_mouth\\_pain.pdf](http://cancer.org/pdf/booklets/ccc_mouth_pain.pdf)

**For a review article published in the Journal of Supportive Oncology, "New Strategies for Management of Oral Mucositis in Cancer Patients:"**

[www.supportiveoncology.net/journal/0402s1.html](http://www.supportiveoncology.net/journal/0402s1.html)

**For clinical practice guidelines from the Multinational Association of Supportive Care, click on "Mucositis" at [www.mascc.org](http://www.mascc.org)**

**For information from the National Cancer Institute:**

[www.cancer.gov/CancerTopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5](http://www.cancer.gov/CancerTopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5)

head and neck cancer patients undergoing radiotherapy yielded contradictory results.<sup>24</sup> A clinical trial is examining GM-CSF mouth rinses to prevent and treat oral mucositis in patients undergoing radiotherapy for head and neck cancer,<sup>25</sup> despite their lack of efficacy in the stem cell transplant population.<sup>26</sup>

■ Saforis is an oral formulation of glutamine that is under review by the US Food and Drug Administration. It has been shown to be effective in reducing the incidence of mucositis in breast cancer patients undergoing standard dose adjuvant chemotherapy. It has not been studied in individuals with head and neck cancer or in patients receiving radiotherapy.

■ Other agents being investigated for the prevention, treatment, and symptom management of mucositis in head and neck cancer patients include vitamins, curcumin, aloe vera, and cytokines; however, conflicting or insufficient evidence exists to recommend for or against them.

## Conclusion

Mucositis is a common complication of radiotherapy to the head and neck region that occurs in up to 100% of patients. No agents have been definitively shown to reduce the incidence and severity of oral mucositis associated with head and neck cancer treatment. International guidelines promulgated by MASCC/ISOO can help guide the development of institution-based oral care protocols, which should emphasize regular assessment, good oral hygiene, and pain and symptom management and should incorporate the use of other targeted interventions (such as topical and intravenous preventative agents) if and when the evidence for their efficacy accumulates.

## References

1. Dodd MJ. The pathogenesis and characterization of oral mucositis associated with cancer therapy. *Oncol Nurs Forum* 2004;31(4 suppl):5-11.
2. Rubenstein EB, Peterson DE, Schubert

M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004;100(9 suppl):2026-2046.

3. Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma: risk factors and clinical consequences. *Cancer* 2006;106:329-336.

4. Duncan M, Grant G. Review article: oral and intestinal mucositis—causes and possible treatments. *Aliment Pharmacol Ther* 2003;18:853-874.

5. Armstrong JA, McCaffrey R. The effects of mucositis on quality of life in patients with head and neck cancer. *Clin J Oncol Nurs* 2006;10:53-56.

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.

7. Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer* 2003;98:1531-1539.

8. 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.

9. Barasch A, Peterson DE. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. *Oral Oncol* 2003;39:91-100.

10. Avritscher EB, Cooksley CD, Elting LS. Scope and epidemiology of cancer therapy-induced oral and gastrointestinal mucositis. *Semin Oncol Nurs* 2004;20:3-10.

11. Eilers J, Epstein JB. Assessment and measurement of oral mucositis. *Semin Oncol Nurs* 2004;20:22-29.

12. Eilers J, Berger AM, Petersen MC. Development, testing, and application of the oral assessment guide. *Oncol Nurs Forum* 1988;15:325-330.

13. Stricker CT, Sullivan J. Evidence-based oncology oral care clinical practice guidelines: development, implementation, and evaluation. *Clin J Oncol Nurs* 2003;7:222-227.

14. Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Summary of evidence-based clinical practice guidelines for care of patients with oral and gastrointestinal mucositis (2005 update). Available at: [http://www.mascc.org/ktml2/images/uploads/Resource\\_centers/Guidelines\\_table\\_12\\_Oct\\_05.doc](http://www.mascc.org/ktml2/images/uploads/Resource_centers/Guidelines_table_12_Oct_05.doc). Accessed October 9, 2006.

15. Nicolatou-Galitis O, Athanassiadou P, Kouloulis V, et al. Herpes simplex virus-1 (HSV-1) infection in radiation-induced oral mucositis. *Support Care Cancer* 2006;14: 753-762.

16. Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews*. 2006(2):Art. no.:CD000978.

17. McGuire DB, Correa ME, Johnson J, Wienands 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.

18. 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 clinical trial. *Cancer* 2001;92:875-885.

19. McNeil Consumer & Specialty Pharmaceuticals. Clinical Study Report: Benzydamine HCl 0.15% Oral Rinse. Available at: [http://download.veritasmedicine.com/PDF/CR002491\\_CSR.pdf](http://download.veritasmedicine.com/PDF/CR002491_CSR.pdf). Accessed August 27, 2006.

20. Buentzel J, Micke O, Adamietz IA, Monnier A, Glatzel M, de Vries A. Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized placebo-controlled phase III study. *Int J Radiat Oncol Biol Phys* 2006;64:684-691.

21. National Institutes of Health (NIH). A study of palifermin for the reduction of oral mucositis in subjects with advanced head and neck cancer. Available at: <http://www.clinicaltrials.gov/ct/show/NCT00131638?order=1>. Accessed August 16, 2006.

22. Finch P, Rubin J. Keratinocyte growth factor expression and activity in cancer: implications for use in patients with solid tumors. *J Natl Cancer Inst* 2006;98:812-824.

23. National Institutes of Health (NIH). A phase II controlled trial of velifermin for prevention of oral mucositis. Available at: <http://www.clinicaltrials.gov/ct/show/NCT00323518?order=1>. Accessed August 26, 2006.

24. Makkonen TA, Minn H, Jekunen A, Vilja P, Tuominen J, Joensuu H. Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a prospective randomized study. *Int J Radiat Oncol Biol Phys* 2000;46:525-534.

25. National Institutes of Health (NIH). GM-CSF mouthwash for preventing and treating mucositis in patients who are undergoing radiation therapy for head and neck cancer. Available at: <http://www.clinicaltrials.gov/ct/show/NCT00293462?order=1>. Accessed August 16, 2006.

26. von Bultzingslowen I, Brennan MT, Spijkervet FK, et al. Growth factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. *Support Care Cancer* 2006;14:519-527.

## ABOUT THE AUTHORS

**Affiliations:** Ms. McGettigan is an oncology nurse practitioner, Department of Medicine, University of Pennsylvania Health System, and Ms. Stricker is an oncology nurse practitioner, Department of Medicine, University of Pennsylvania Health System, Doctoral Candidate & Clinical Associate, University of Pennsylvania School of Nursing, Philadelphia, PA.

**Conflicts of interest:** None disclosed.