Managing the Oral Complications Associated with Chemotherapy and Radiation Therapy

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In This Issue

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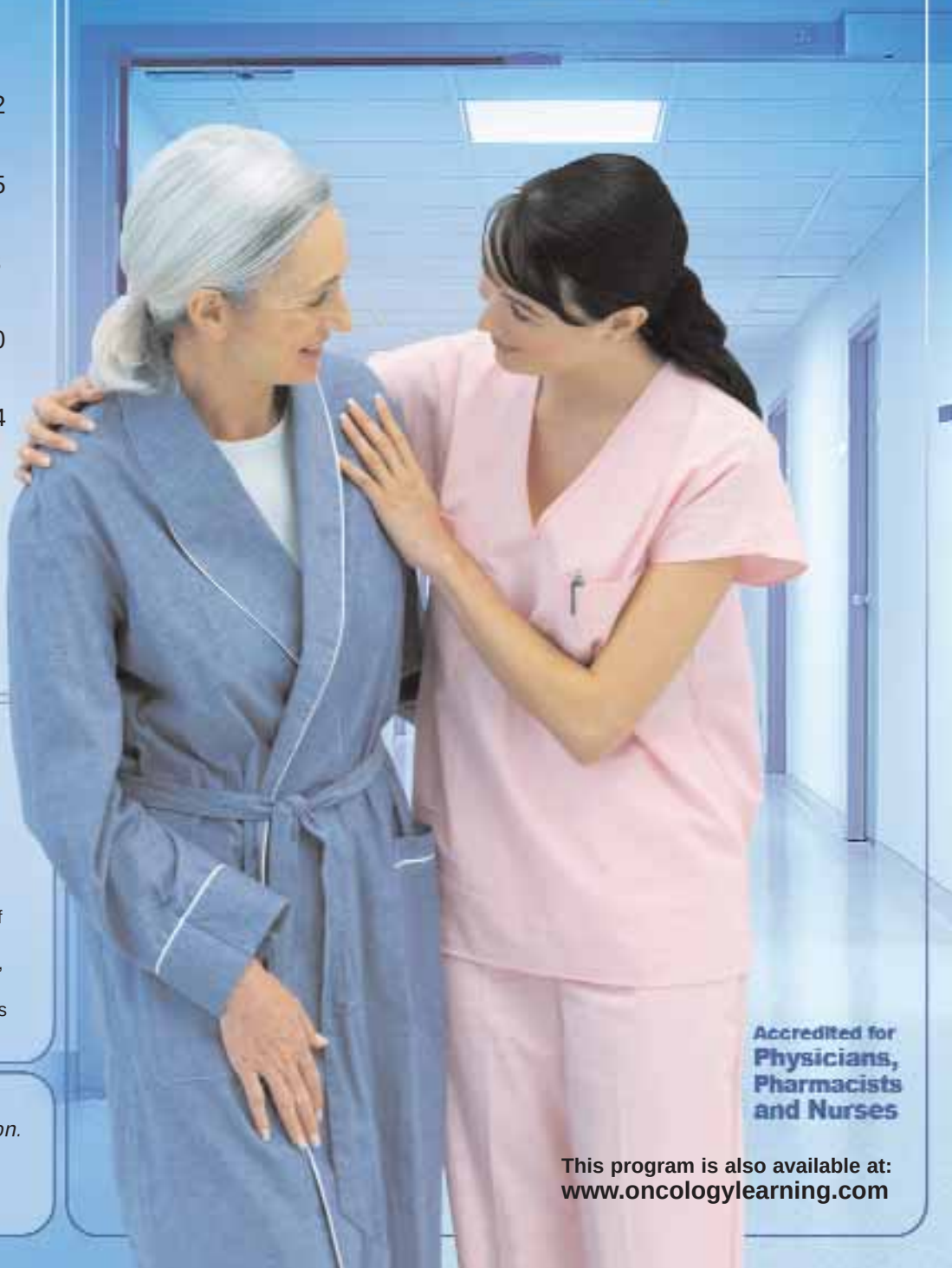

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Educational Objectives

At the conclusion of this program, the participant will be able to:

- Understand the incidence, pathophysiology, clinical presentation and importance of oral mucositis
- Examine oral mucositis scoring/assessment systems and effective treatment action plans
- Identify nutritional considerations in the patient with xerostomia or oral mucositis
- Discuss adequate oral care and its importance in the patient with xerostomia or oral mucositis

Editor's Perspective

Editorial: The Prevalence, Importance, Assessment and Treatment of Oral Mucositis

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The term "oral mucositis" arose in the late 1980s to describe chemotherapy and/or radiotherapy-induced inflammation of the oral mucosa. Despite advances in understanding its pathophysiology, oral mucositis continues to be a debilitating condition manifested by pain, infection, weight loss, economic burden and poor quality of life (QOL). Numerous prevention and treatment strategies have been researched in clinical trials, but most have failed.

Although progress in this arena has been slow, new treatment and prevention techniques for managing oral mucositis are promising. Evidence-based guidelines are emerging to guide practitioners toward proven management protocols that identify pretreatment risk factors, communicate proven oral management protocol, highlight the need for patient education and provide direction for new research. The following articles will address current and emerging strategies for preventing and treating oral mucositis.

Incidence

More than 400,000 patients are affected by this painful and debilitating condition during cancer treatment. Patients with cancer receiving high-dose chemotherapy and irradiation are at significant risk for severe mucositis. The most severe treatment-related risk factors are seen in patients treated with radiation for head and neck cancer (100%) and in hematopoietic stem cell transplant (HSCT) recipients (50%-100%). When chemotherapy and radiotherapy are combined, the incidence of mucositis approaches 100%.[1] The extent of mucositis and its sequelae can become a dose-limiting toxicity that leads to decreased doses or interrupts treatment, placing the patient at risk for continued tumor burden.[2]

In the face of these overwhelming statistics, no standard of care has been universally accepted for managing mucositis. Recently, the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) have published clinical guidelines that can guide clinicians in approved methods for the prevention and treatment of mucositis.[3,4] A full discussion of these guidelines is discussed later in this newsletter.

Clinical Presentation

Patterns of clinically evident oral mucositis vary with the cancer therapy delivered, including radiation therapy and chemotherapy, the myelosuppressive agent used and the dose and duration of treatment. Generally, patients receiving multiagent chemotherapy demonstrate oral mucositis from day 4 to day 5, with symptoms peaking around day 12. Patients receiving concomitant chemotherapy and radiation therapy have increased severity and duration of mucositis. Symptoms appear around day 5 or 6, but may continue for several weeks. HSCT recipients show oral mucositis from days 7 to 11, while symptoms may persist for 2 to 3 weeks. Those recipients who experience continued, severe immunosuppression, or whose course is complicated by graft vs host disease (GVHD), will have a longer course.[5,6]

Economic Implications

A growing body of literature is emerging about the costs of managing mucositis during or shortly after cytotoxic therapy. Researchers have found that the economic burden is significantly higher in patients with mucositis when compared to those without mucositis. Sonis et al. reported clinical and economic outcomes of mucositis in 95 HSCT recipients and found that additional days

of fever, infection, use of total parenteral nutrition (TPN) and injectable narcotics led to 2.5 additional days in the hospital. Mean hospital charges were $42,749 higher among patients with evidence of ulceration compared with those without mucositis (*P* =.06).[7] A more recent and larger study (N = 281) conducted in the allogeneic HSCT setting supports similar findings. The worst mucositis noted was associated with a higher number of days of TPN and parenteral narcotic therapy, increased number of hospital days, fever and incidence of significant infection.[8] Researchers acknowledge that the costs sustained by HSCT recipients can be extrapolated to the overall cost of mucositis among patients with solid tumors. In doing so, the overall cost in this setting would far exceed the overall cost among transplant recipients.

> Mucositis dramatically impacts a patient's quality of life (QOL) during and after the occurrence.

Research has also underscored the importance of older and low cost methods to decrease the symptoms of mucositis. Cryotherapy, used for 30 minutes before administering bolus 5-fluorouracil (5-fu) has been found to be effective in reducing mucositis.[9] A more recent study in HSCT patients receiving melphalan supported similar findings.[10]

Clinical Presentation

Mucositis targets the cellular elements of the mucosal epithelium, connective tissue and vasculature. These effects progress to thinning of the epithelium and ulceration of oral soft tissues. The most common areas affected are the buccal and labial mucosa and ventral and lateral surfaces of the tongue, soft palate and floor of the mouth. The appearance of the affected area ranges from mild erythema to severe ulceration.[11] The classic symptoms of mucositis are characterized by pain, ulceration and dysphagia. The clustering of these symptoms often result in communication impairment and reduction of oral intake with concomitant weight loss. Mucositis in the severely immunocompromised patient can lead to opportunistic bacterial, viral and fungal infections, including sepsis. Ruescher et al. noted HSCT recipients with ulcerative mucositis were 3 times as likely to develop alpha hemolytic streptococcal bacteremia as those without ulcerative mucositis. Patients with this condition required an additional 6 days of hospitalization, resulting in an additional charge of $4500 per day.[12] Late effects on the oral cavity are noted to be a thinning of the oral mucosa resulting in chronic and non-healing ulcers that may progress to soft tissue loss.[13]

Quality of Life

Mucositis dramatically impacts a patient's QOL during and after the occurrence of mucositis, and few studies have rigorously examined this issue. The major clinical factors cited above lead to functional impairment. These consequences may result in sadness, tension or feeling of isolation.[14] Epstein et al. conducted an investigation to assess the QOL, oral function and oral symptoms following radiotherapy. Six months following therapy, patients reported difficulty in chewing and eating (43%), dry mouth (91.8%), changes in taste (75.4%), dysphagia (63.1%), altered speech (50.8%), difficulty with dentures (48.5%) and increased tooth decay (38.5%). Pain was common

(58.4%), interfered with chewing and eating (43%) and hampered daily living activities.[14] In another study, Dodd et al. compared QOL and effective changes of patients receiving chemotherapy who developed oral mucositis to those who did not. Patients who developed mucositis showed an increase in total mood disturbance. Depression and anger subscale scores doubled in patients who had mucositis.[15]

In a prospective study of 6 patients undergoing intensive cytotoxic therapy for HSCT, patients had these comments: "I'd say mucositis was the worst thing that happened;" "I feel like I have razor blades in my mouth;" "Anguish in the belief that eating is necessary for survival, yet not wanting to eat;" and "Feeling tired and not wanting to talk." Patients also commented on their inability to enjoy life by the loss of simple pleasures such as eating and drinking. As the authors conclude, oral mucositis is more than a sore mouth.[16] These comments present us with a "snapshot" of the effect mucositis has on QOL.

Care Issues and Updates

Research-based clinical guidelines discussed below can guide practitioners to the optimal approach for diminishing the effects of mucositis. Among these approaches is identifying mucositis risk factors before the patient begins therapy. All patients receiving chemotherapy, radiation or both, along with HSCT candidates, can benefit from dental examinations to identify complicating factors for oral mucositis. These include poorly fitting dentures, orthodontic devices or periodontal disease. Patient education is imperative to ensure patients and their caregivers understand the importance of ongoing oral care during and after treatment. The health care team working with patients at risk for mucositis can reduce its intensity by being aware of new approaches to mucositis, patient teaching techniques and emerging products to treat mucositis.

Dr. John Inzerillo offers a comprehensive review of evidence-based management of mucositis in this newsletter. Basic oral hygiene is one of the most important methods that may help reduce the complications of oral mucositis. It is often neglected, perhaps because the treatment is inexpensive and relatively easy to do. Practitioners give more reasons for its being overlooked and undervalued:

- We are too busy to teach patients
- The patient is too tired to do essential mouth care
- It is too painful for the patient to comply
- Magic mouthwash works better!

The economic, clinical and QOL benefits of effective treatment and prevention protocols for mucositis will challenge clinicians to remain current in their understanding of this issue.

As it pertains to “magic mouthwash”, it is clear that there is no standard formula for magic mouthwash. It differs among ingredients that have been determined to be of questionable value, including lidocaine, diphenhydramine and magnesium and aluminum hydroxide.

Clinician awareness and patient teaching are critical to the success of effective mouth care. Although little has been researched in terms of the effectiveness of follow-up care, clinicians are aware of the need for continued teaching and assessment across the continuum of cancer therapy.

Research Update

Sonis et al. have determined that the pathophysiology of mucositis includes 5 stages, each stage having its unique molecular pathways. Research is now focused on the development of mechanistic agents to target specific biologic events that block or target inflammatory cytokines causing mucositis rather than a one-size-fits-all approach. Agents under research include sargramostim, molgramostim, herbavis, whey growth factor extract, teduglutide, insulin-like factor I and PV-701.[17]

The economic, clinical and QOL benefits of effective treatment and prevention protocols for mucositis will challenge clinicians to remain current in their understanding of this issue. Until novel agents become available, healthcare providers practicing in cancer treatment centers must also remain current in their management of other sequelae, including xerostomia, nutritional deficiencies and reduced patient functioning. Finally, it is just as important to stay abreast of a growing number of agents for mucositis that should, perhaps, not be used. Old ways die hard and many institutions are wed to specific protocols that are no longer acceptable. The intent of this editorial, and the series of important articles that follow, is to give you the opportunity to review, and perhaps, revise your practice. In so doing, we all benefit. Good reading.

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Risk Factors and Causes of Oral Mucositis

Our understanding of the pathogenesis of mucositis has exploded over the past 5 years to give us new insights into improved therapies for this almost

ubiquitous complication of chemotherapy and radiation therapy.[1] Oral mucositis will develop in up to 40% of patients treated with conventional chemotherapy and up to 70% of patients receiving conditioning regimens for BMT.[2] In patients undergoing total body irradiation and/or high-dose myeloablative chemotherapy for stemcell transplantation, mucositis occurs at a frequency of 50% to 100%.[3] Severe occurrences of mucositis occur during combination chemoradiotherapy in practically all patients treated for head and neck cancer.[4]

For conventional chemotherapy, the degree of mucosal toxicity depends on the particular chemotherapeutic agent used, the specific regimen employed, the duration of therapy and dose intensity. For example, 5-fu, a commonly used agent for the treatment of colon and breast cancer, is associated with rates of grade 3-4 mucositis exceeding 15%. The rate increases (> 20%) when drugs such as topotecan or etoposide are used in combination regimens. When radiation is administered concurrently with 5-fu, the rates of grade 3-4 oral mucositis can exceed 30%.[1] As it pertains to radiation therapy alone, the degree and duration of mucositis is related to the radiation source, the dose per fraction, fractions per day, concomitant boost, volume of irradiated tissue and tissue tolerance.[5]

High-dose chemotherapy combined with radiation therapy, as administered for allogeneic BMT, causes significant changes in the integrity of the mucosal epithelium. These changes are more likely to occur with allogeneic than with autologous transplant due to the higher doses of chemotherapy administered and the total body irradiation often employed as a conditioning regimen for allogeneic transplant. Here the rates of grade 3-4 mucositis exceed 60%, which is similar to rates seen in patients receiving methotrexate for GVHD prophylaxis. This is supported by the results obtained in 1999 by Rapoport et al. whereby individuals who received marrow-derived stem cells, unrelated or sibling donor grafts or had a diagnosis of acute myelogenous leukemia or myelodysplastic syndrome had higher grades of mucositis. In addition, drugs used in transplant preparative regimens, such as busulfan and cyclophosphamide, are associated with significant mucositis.[1,6]

Other frequently used chemotherapeutic agents can cause mucositis due to endothelial toxicity and apoptosis of the mucosal basal cells. These drugs include 5-fu, cisplatin, melphalan, cytarabine (Ara-C) and etoposide. These agents have many uses. For example, 5-fu is most commonly used to treat colon and rectal cancers (in combination with radiation therapy), but is also used to treat gastric cancer, head and neck cancer (also in combination with radiation therapy) and pancreatic cancer. Cisplatin is most commonly used to treat lung cancer, often used with etoposide. It is also used to treat bladder and pancreatic cancers. Ara-C is used to treat acute leukemia and causes significant mucositis since it is initially administered over a 7 day period.[7]

It was previously believed that direct damage by chemotherapy and/or radiation to the basal layer of the mucosa cells leads to loss of the renewal capacity of the epithelium. This leads to mucosal cell death, atrophy and ulceration. The presence of ulceration leads to bacterial, viral or fungal invasion and often, as a progression of this process, sepsis, malabsorption, diarrhea, bleeding and pain.[1]

With greater understanding in the field of molecular biology, there is now further evidence suggesting that mucositis is more than an epithelial process. From animal and human studies, researchers have the capacity to study the relationship between proinflammatory cytokines and mucosal toxicity. It is now known that increased levels of tumor necrosis factor-alpha (TNF-α) and interleukins-1 and -6 (IL-1 and IL-6) correlate with the extent of nonhematologic toxicities in patients following chemotherapy.[8] These indirect effects on the mucosal barrier occur simultaneously with direct effects and contribute to barrier damage.

The current theory used to explain the global changes involved in the initiation and progression of mucositis includes the following 5 stages: initiation, upregulation and generation of messenger signals, signaling and amplification and ulceration and healing.[1]

Stage 1
The first step leading to the development of mucositis is the generation of oxidative stress and reactive oxygen species (ROS), or free radicals. This process is known as *initiation*. Experiments have shown that mucosal injury can be attenuated by blocking the production of free radicals produced by chemotherapy or radiation.[9]

Stage 2
During the second phase, upregulation and generation of messenger signals, a number of synchronous events occur.

ROS generated in the first step cause direct damage to DNA and, therefore, death of basal epithelial cells. It is now believed that the activation of a transcription factor, nuclear factor-κB (NF-κB) causes upregulation of the genes that are responsible for the production of proinflammatory cytokines such as TNF-α, IL-1β and IL-6. This leads to tissue injury and apoptosis, or programmed cell death. Other pathways involved in the tissue injury response include the activation of sphyngomyelinase by ROS, the activation of ceramide synthase by chemotherapy (leading to primary apoptosis) and macrophage activation that leads to the production of matrix metalloproteinases that directly cause more tissue damage and increased production of TNF-α.[10]

Stage 3

The signaling and amplification phase is characterized by positive feedback loops that augment the production of proinflammatory cytokines. The damaging events at this time are still focused on the submucosa and basal epithelium; therefore, the appearance of the mucosa remains normal.[1]

Stage 4

It is in the fourth phase when the actual ulceration of the mucous membranes occurs. It is also the most symptomatic phase for the patient and usually occurs 1 week after chemotherapy. Because the ulcer is a focus of bacterial contamination, secondary infection is common and can lead to bacteremia and sepsis in the neutropenic patient. Yeast infections and reactivation of herpes simplex viral infection may also occur secondary to immunosuppresion.[11]

Stage 5

The final phase, healing, typically occurs from days 12 to 16 after the last chemotherapy treatment. It leads to the renewal of epithelial proliferation and repopulation of the normal oral flora. This phase, when mucositis is associated with the administration of chemotherapy, is usually associated with neutrophil recovery. It is also dependent on resolution of infection and/or mechanical irritation, which may take longer to resolve in patients receiving radiation to the head and neck region.[11]

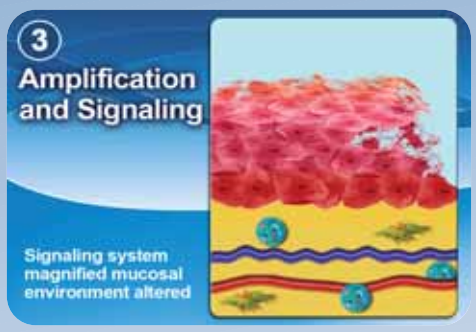
The clinical presentation of mucositis occurs in a predictable manner, usually affecting the movable nonkeratinized mucosa of the soft palate, cheeks and lips, the ventral surface of the tongue and the floor of the mouth. The gingiva, dorsal surface of the tongue or the hard palate are rarely affected, probably due to their slower rate of proliferation. Erythema, ulcers and pseudomembranous ulcerations can be seen with ulceration size ranging from a few millimeters to a few centimeters long. Bleeding from the ulcerations may also occur, particularly in the presence of chemotherapy-induced thrombocytopenia.[12]

In clinical practice, not everything that looks like mucositis is mucositis, especially in populations that undergo HSCT. A prevalent complication seen in this group includes acute GVHD, a condition

Pathobiology of Mucositis

The Initial Stage of Mucositis. Radiation and chemotherapy generate reactive oxygen species with cells causing direct damage to cells, tissues and vessels.

Upregulation and Messenger Generator. Activation of NF-kB, proinflammatory cytokines, Il-6, IL-1β and TNF-α causing tissue injury.



Signaling and Amplification. TNF-α leads to production of NF-kB causing altered mucosal environment. Tissue may appear normal.

Ulceration. Bacterial colonization occurs with release of macrophages causing more production of Il-6, IL-1β and TNF-α.

Healing Extracellular Matrix Signal Initiates the Healing Process. Oral mucosa is altered leading to increased risk of mucositis in the next cycle of treatment.

that can target areas, including the mouth, skin and gastrointestinal tract. GVHD and mucositis are confounding situations that require skilled assessment; chronic GVHD of the mouth can be confirmed by biopsy 60 to 90 days posttransplant. For those patients receiving allogeneic transplantation, the prevalence of GVHD ranges from 18% to 70%.[13] Similar to mucositis, acute GVHD of the mouth can present as ulcers, desquamation or bullae (large, fluid-filled blisters). Acute GVHD can appear at any time up to 120 days post-transplant. Chronic GVHD occurs approximately 70 days post transplantation in 33% to 44% of allogeneic BMT HSCT patients.[14] Therefore, as an important clinical reminder, if OM is not healing, GVHD should be considered.

Herpes simplex virus (HSV) infections must be included in the differential diagnosis; although, a patient does not need to undergo HSCT to reactivate HSV. Reactivation of HSV infection can occur following conventional chemotherapy or intensive chemotherapy with or without HSCT support. The use of prophylactic acyclovir has been shown to be very effective at reducing the amount of HSV reactivation, from 80% to less than 5%, among BMT recipients who are HSV seropositive.[15] Acyclovir (250 mg/m^2/dose IV q8h or 125 mg/m^2/dose IV q6h) should be started when initiating the conditioning regimen and it should continue until mucositis has markedly improved or disappeared and with engraftment.[16]

Currently, there has been a resurgence of acyclovir- and foscarnet-resistant HSV infection in the BMT population. It appears that the prolonged immunodeficiency associated with lymphocyte depletion of the graft strongly predisposes to drug-resistant HSV infection.[17] Herpetic mucositis is more often seen in patients receiving radiation (as high as 30% of patients) or standard doses of chemotherapy.[18] Herpetic lesions are seen usually in both keratinized and nonkeratinized areas of the mouth. Keratin is a sulfur-containing fibrous protein that is the basis for horny epidermal tissues such as skin, hair or nails. It is typically indigestible by gastrointestinal enzymes. The lining cells of the oral cavity are known to have regional variations in their degree of keratinization. The hard palate is highly keratinized, while the ventral portion of the tongue and cheeks are not keratinized. The gingiva and the dorsal surface of the tongue have a moderate degree of keritinization. The herpetic lesions associated with mucositis can present as ulcerative or vesicular lesions. All such lesions should be cultured since they predispose patients to secondary infections.[17]

There are certain patient-related risk factors that will predispose a patient to develop mucositis, with smoking and alcohol consumption being potential targets for patient teaching.[19] Other predisposing factors include xerostomia, or dry mouth, that can be seen in such autoimmune conditions as Sjögren's Syndrome or lupus. On the individual level, deficiencies of certain metabolic enzymes, such as dihydro-pyrimidine dehydrogenase (this enzyme metabolizes 5-fu) will lead to mucosal toxicity involving the entire gastrointestinal tract. Deficiencies of either B12 or folate will also lead to mucositis, as both of these vitamins are required for DNA synthesis.[20]

Other preventable conditions, such as tooth decay, poor dental hygiene, ill-fitting or over-use of dentures and dehydration will also lead to higher grades of mucositis.[21,22] This is where patient education becomes important, since some of the more debilitating effects of therapy may be reduced with proactive attention.

The advances over the past 5 years in the fields of genetics and molecular biology, particularly in the arena of signal messaging and cytokine interaction, have led us to a greater understanding of the pathobiology of mucositis. It is up to us as clinicians to be aware of the mechanisms and consequences of the therapies we employ and to educate our patients and enable them to be active participants along the path toward recovery.

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Oral Mucositis: Patient Assessment

John Inzerillo, MD

Chemotherapeutic advances have enhanced the treatment of patients with cancer and the newer monoclonal antibody therapies (ie, rituximab [RITUXAN®], trastuzumab [HERCEPTIN®], bevacizumab [AVASTIN®],) and targeted therapies sorafenib [NEXAVAR®] and sunitinib [SUTENT®]) have met their promise of reduced toxicity. However, medical researchers now know that one particular class of drug probably will not single-handedly rid humanity of cancer, nor eliminate adverse effects of therapy. Therefore, patients receiving chemotherapy and/or radiation therapy, as well as their health care providers and family caregivers, must be prepared to confront

the ongoing, important issue of mucositis.

In the daily practice of clinical oncology, when describing treatment related toxicity, we have to do better than say, "the mucous membranes look very bad." A better indication of severity would include a modifier, such as mild, moderate or severe. In order to be more accurate and specific in our descriptions of mucositis, a number of assessment scales have been developed, each taking a unique approach to achieving the objective of grading mucositis.

Ideally, scales used to assess oral mucositis should be objective, sensitive and reproducible. They should also require minimal training and possess intrarater and interrater reliability.[1] The most widely used and relevant scales are based on the National Cancer Institute (NCI) and the World Health Organization (WHO) models. In a review of 400 clinical trials, it was determined that 43% used the NCI scales and 38% followed the WHO scales.[2]

The National Cancer Institute's Common Toxicity Criteria Manual Version 2 (NCI CTC v.2) scale for chemotherapy-induced mucositis utilizes the following grading system[3]:

- Grade 0 – No mucositis
- Grade I – Painless ulcers, erythema or mild soreness in the absence of ulcers
- Grade II – Painful erythema, edema or ulcers, but eating is possible
- Grade III – The same as Grade II but patient requires IV hydration
- Grade IV – Severe ulceration or requiring parenteral or enteral nutritional support
- Grade V – Death related to toxicity

The major cooperative groups involved in clinical research in the United States, such as the Cancer and Leukemia Group B (CALGB), National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Southwest Oncology Group (SWOG), utilize this NCI scale because the clinical studies are sponsored by the NCI. This is a user-friendly scale because little training is required.

It should be noted that the NCI has a distinct scale regarding mucositis secondary to BMT. Grades 0, I, II and III toxicities are the same for each modality (chemotherapy-induced and HSCT). However, to incur a Grade IV mucosal toxicity during transplantation, a patient must experience severe ulceration requiring prophylactic intubation for respiratory support or have a documented aspiration pneumonia.[3]

The NCI CTC v.2 also contains a separate section for the toxicities associated with radiation therapy. The radiation-related adverse events are divided into those that are acute (within the first 90 days of therapy) and delayed (after the first 90 days of treatment therapy). The adverse events included in NCI CTC v.2 are: radiation dermatitis, radiation recall reaction, dysphagia-esophageal related to radiation, dysphagia-pharyngeal related to radiation, mucositis due to radiation and pain due to radiation.[3]

Both the NCI CTC and the WHO Scale measure anatomical and functional components of mucositis. The WHO Oral Toxicity Scale includes such components as visible ulcers, the presence of pain or soreness and swallowing ability. The grading system is as follows[4]:

- Grade 0 – None
- Grade I – Soreness and/or erythema with no ulceration
- Grade II – Erythema, ulcers but patient can eat a solid diet
- Grade III – Ulcers, extensive erythema and cannot swallow a solid diet
- Grade IV – Alimentation is not possible

Both scales are less than ideal, since neither scale makes note of mucosal color change, such as pallor, white patches, discolored lesions or mucosal moisture changes reflecting salivary impairment. Additionally, there is no mention of oral cleanliness, bad odor, tooth discoloration, mucosal cracks, fissures or blisters. These 2 well-used scales also lack comments on the actual character of mucosal lesions, such as position, clustering or confluence. Finally, no mention is made of the presence of edema of the lips, tongue or mucosa.[5] While these scales combine clinical tissue change with symptoms and function, the practitioner might find them too cumbersome for daily use.

Before discussing other mucositis severity assessment scales, it is important to note an update to the NCI CTC scales. Specifically, the NCI released the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) scale in 2003 and updated it in 2006. This latest incarnation of the NCI CTC scale, specifically addressing the upper aerodigestive tract, is graded as follows[6]:

- Grade I – Minimal symptoms, normal diet, minimal respiratory symptoms not interfering with function
- Grade II – Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with activities of daily living (ADL)
- Grade III – Symptomatic and unable to

adequately aliment or hydrate orally; respiratory symptoms interfering with ADL
- Grade IV – Symptoms associated with life-threatening consequences
- Grade V – Death

Another toxicity scale that has been used to assess mucositis, though less frequently than the NCI CTC and WHO scales, is the Western Consortium for Cancer Nursing Research (WCCNR) scale. One of its limitations is that it was originally designed to assess mucositis as a result of chemotherapy only; it was not intended to rate mucositis due to radiation therapy.[7] This scale uses subjective determinations of the color of mucosal lesions, the number of lesions and the presence or absence of blood on the mucosa.

In the early 1980s, the Radiation Therapy Oncology Group (RTOG) developed a radiation-specific acute toxicity grading system known as the RTOG Acute Radiation Morbidity Scoring Criteria. This system was upgraded in 1984 to include the late effects of radiation and was updated again in 1995.[8] Scoring systems are in a constant state of flux in an effort to gain greater accuracy.

As we can see in reviewing each of the toxicity scales presented, there are many similarities among them. In fact, the NCI CTC and the WHO scales are essentially identical. The RTOG scale does not allow for disruption in alimentation and it requires that mucosal lesions be measured. It shares the descriptors of bleeding vs absence of bleeding with the WCCNR scale.

There are a variety of other useful scales available to rate mucositis. The Oral Mucositis Assessment Scale (OMAS) utilizes the degrees of ulceration and erythema measured in specific areas of the mouth. Secondary indicators include oral pain, dysphagia and the patient's subjective ability to eat. While OMAS has been assessed for validity, reliability and use by observers of various training and background, one of the downsides of this scale is that in-depth training for raters and calibration of the scores among raters is essential. Also of note is that the OMAS is not sensitive to low grades of oral mucositis.[1] This scale is cumbersome to use in clinical practice and is usually reserved for in-depth research work.

When presented with a patient who is to undergo chemotherapy, radiation therapy, both or BMT, it is useful to be aware of risk factors that will lead to increased grades of mucositis. Individuals with body mass indexes (BMI) >25 have higher grades of mucositis. Overweight is defined as a BMI between 25.0 and 29.9, while obesity is defined as a BMI $\geq$ 30. The reason for the higher grades of mucositis is that patients who weigh more will receive more drug, as dose is calculated by height and weight (ie, mg/m^2).[9] The ratio of adipose to lean body weight is increased in individuals with higher body weight and this may affect drug distribution and pharmacokinetics.[10]

Moving forward, our work is to enhance our understanding of the pathophysiology of mucositis, develop increasingly effective patient assessment tools and effectively prevent, minimize and manage adverse effects of therapy.

Other uncontrollable risk factors that increase the grade of mucositis are baseline neutrophil count <4000 cells/mm^3 and xerostomia (dry mouth).[11] There are also patient-related risk factors for mucositis in patients receiving chemotherapy and radiation therapy, including pre-existing dental problems (gingivitis, periodontal disease, dental plaques, dental caries, faulty restorations and improperly fitting prostheses), consumption of irritating substances (alcoholic beverages) and younger age.[12,13,14] The proliferation rate of basal cells comprising the mucosal lining in children is higher therefore, they are 3 times more likely to experience mucositis compared with the elderly.[14] Other studies show variable experience of mucositis in children and, overall, it appears risk is not different than adults when similar diagnoses and cancer therapies are used.

Cancer will touch 1 in 3 lives. With ongoing advances in care, many will count themselves among the growing number of cancer survivors. However, to achieve that end, many individuals will undergo chemotherapy and/or radiation therapy and will therefore experience their resultant toxicities. Moving forward, our work is to enhance our understanding of the pathophysiology of mucositis, develop increasingly effective patient assessment tools and effectively prevent, minimize and manage adverse effects of therapy. While no individual mucositis assessment scale is perfect, the important point to note is that frequent and ongoing assessment of the oral cavity is imperative to effective patient care.

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Oral Mucositis: Treatment Action Plans

The Mucositis Study Group of MASCC and ISOO recently published an update to their clinical practice guidelines for the prevention and treatment of mucositis.[1] The original guidelines, published in 1994 as a 2-article supplement in the journal *Cancer*,[2,3] presented the findings of a 36-member panel of experts who reviewed evidence-based literature published between January 1966 and May 2002. The updated guidelines incorporated literature published from January 2002 to May 2005. In developing the guidelines, the systematic weighting of both level and grade of evidence were based on criteria of the American Society of Clinical Oncology (Table 1).[4]

Significant revisions to the guidelines for the treatment of oral mucositis are presented in Table 2.[1] It is interesting to note, several "do not use" recommendations have been incorporated into the guidelines (antimicrobial lozenges, sucralfate, GM-CSF mouthwashes). Oral mucositis treatment recommendations continuing from the original guidelines include benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy, patient-controlled analgesia with morphine in patients undergoing HSCT and low-level laser therapy (LLLT).

Systemic Treatment

The most significant pharmaceutical addition to the guidelines as they pertain to oral mucositis is palifermin (Kepivance®; Amgen). Palifermin is a human keratinocyte growth factor (KGF), an endogenous protein in the fibroblast growth factor (FGF) family that binds to the KGF receptor, resulting in proliferation, differentiation and migration of epithelial cells in many tissues including the tongue and buccal mucosa. Palifermin is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. The safety and efficacy of palifermin have not been established in patients with nonhematologic malignancies, since its effects on stimulation of KGF receptor-expressing, nonhematopoietic tumors in patients are not known.[5]

Spielberger et al.[6] conducted a double-blind study comparing the effects of palifermin with placebo on the development of oral mucositis in 212 patients with hematologic cancers. Patients were evenly divided between the palifermin treatment and placebo groups and the baseline characteristics of the patients were similar. Palifermin treatment significantly reduced the incidence of WHO grade 3 or 4 mucositis vs placebo (63% vs 98%); the median duration of oral mucositis of grade 3 or 4 among patients with this adverse effect (6 days vs 9 days); and the median duration of oral mucositis of grade 3 or 4 among all patients (3 days vs 9 days). The incidence of WHO grade 4 mucositis was 20% among patients receiving palifermin vs 62% in the placebo-treated group. The median duration of grade 4 oral mucositis was significantly reduced among the 21 palifermin recipients than among the 66 placebo recipients with this adverse effect (2 days vs 6 days). Palifermin treatment also conferred a reduced median duration of grade 2 oral mucositis or higher (8 days vs 14.3 days).

Patients receiving palifermin should be advised of possible mucocutaneous adverse effects, including rash, erythema, edema, pruritis, oral/perioral dysesthesia, tongue discoloration, tongue thickening and alteration of taste. Palifermin should not be administered within 24 hours before, during or within 24 hours after administration of myelotoxic chemotherapy, as this may result in increased severity and duration of oral mucositis.[5]

The recommended dose of palifermin is 60 mcg/kg/day, administered as an IV bolus injection for 3 consecutive days before (to be completed 24 to 48 hours prior to myelotoxic therapy) and 3 consecutive days after myelotoxic therapy (on the same day of hematopoietic stem cell infusion, but at least 4 days after the most recent administration of palifermin) for a total of 6 doses. The product is available in a 6.25-mg vial, which is to be reconstituted with 1.2 mL of sterile water, resulting in a solution with a concentration of 5 mg/mL. The contents of the vial should be swirled gently, not shaken or agitated, and the final solution should not be filtered during preparation or administration. The dose is administered as an IV bolus.[5]

Dry Mouth Management

Other agents of interest in maintaining adequate moisture in the oral cavity include Salagen®, Evoxac®, Gelclair® and Caphosol®. Salagen® (pilocarpine hydrochloride tablets; MGI Pharma) is indicated for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck and for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome. Pilocarpine is a cholinergic parasympathomimetic agent exerting predominantly muscarinic action. This increases secretions by exocrine glands (salivary, sweat, lacrimal, gastric, pancreatic, intestinal and pulmonary).[7]

Several studies have demonstrated the efficacy of oral pilocarpine in reducing xerostomia symptoms and improving saliva production in patients with head and neck cancer[8,9] and in patients with Sjögren's Syndrome.[10,11] In head and

neck cancer patients, the recommended initial dose of SALAGEN is 5 mg 3 times daily. Dosage should be titrated according to therapeutic response and tolerance. The usual dosage range is 15 to 30 mg daily, not to exceed 10 mg per dose. Although early improvement may be seen, at least 12 weeks of uninterrupted therapy may be required to assess if a beneficial response will be achieved. The lowest tolerated dose should be used for maintenance therapy as the incidence of adverse events increases with dose.[7]

Evoxac® (cevimeline; Daiichi) is also a cholinergic agonist. While Evoxac® is not FDA-indicated for use in head and neck cancer patients as is Salagen®, its mechanism of action and, thereby, rationale for use, is similar. Evoxac® is contraindicated for use in patients with uncontrolled asthma, known hypersensitivity to cevimeline and when miosis is undesirable (acute iritis and in narrow-angle [angle-closure] glaucoma). It should be used with caution in patients with a history of cardiovascular disease (angina pectoris, myocardial infarction), controlled asthma, chronic bronchitis or chronic obstructive pulmonary disease. Patients should be informed that cevimeline may cause visual disturbances, especially at night, that could impair their ability to drive safely. Similar precautions should be employed when using Salagen® tablets for this indication. The recommended dose of cevimeline is 30 mg 3 times daily.[12]

The NCI states the management of oral mucositis via topical approaches should address efficacy, patient acceptance and appropriate dosing. A stepped approach should be utilized, with progression as follows[13]:

- Bland rinses (e.g., 0.9% normal saline and/or sodium bicarbonate solutions)
- Mucosal coating agents (eg, antacid solutions, kaolin solutions)
- Water-soluble lubricating agents, including artificial saliva
- Topical anesthetics (eg, viscous lidocaine, benzocaine sprays/gels, dyclonine rinses, diphenhydramine solutions)
- Cellulose film-forming agents for covering localized ulcerative lesions (eg, hydroxypropyl cellulose)

Many practitioners employ a "magic mouthwash," typically consisting of lidocaine, diphenhydramine and magnesium and aluminum hydroxide (Maalox®). However, in a randomized trial of the efficacy of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis, Dodd et al.[14] found no significant differences in time for cessation of the signs and symptoms of chemotherapy-induced mucositis among 200 patients treated with either salt and soda, chlorhexidine or "magic mouthwash" (lidocaine, diphenhydramine and Maalox®). This finding was mirrored by Shih et al.[15] who conducted a Medline® search of the literature from 1966 to 2001 and determined the most effective measure to treat radiation therapy-induced mucositis in patients with head and neck cancer is frequent oral rinsing with a bland mouthwash, such as saline or a sodium bicarbonate rinse.

Regarding oral rinses, Caphosol®, a new topical agent (medical device) for use in the treatment of oral mucositis, is an aqueous electrolyte solution containing dibasic and monobasic sodium phosphate, calcium chloride, sodium chloride and purified water. It is designed to resemble human saliva. Caphosol® is indicated for dryness of the mouth or throat (hyposalivation, xerostomia) regardless of the cause and regardless of whether the conditions are temporary or permanent. It is also indicated as an adjunct to standard oral care in treating the mucositis that may be caused by radiation or high-dose chemotherapy.[17] A prospective, randomized, double-blind, placebo-controlled trial evaluated the duration and severity of mucositis and requirements for opioid medications in 95 patients undergoing HSCT. Data demonstrated significant decreases in days of mucositis (3.72 vs 7.20, $P = .001$), days of pain (2.86 vs 7.67, $P = .0001$), dose of morphine (30.46 mg vs 127.96 mg) and days of morphine (1.26 vs 4.02, $P = .0001$) for patients receiving Caphosol® as compared with those receiving placebo.[18]

Caphosol® is prepared by mixing 1 ampule of the phosphate solution (blue ampule – A) with 1 ampule of the calcium solution (clear ampule – B) in a clean glass. The patient should be instructed to swish thoroughly for 1 minute with one-half of the solution and spit out, then repeat with the remaining one-half solution and spit out. The solution should be used immediately after mixing. Caphosol® should be used 4 times daily from the onset of cancer treatment; up to 10 doses per day can be employed if pain from mucositis is experienced. It should be used for the duration of treatment. No adverse effects are anticipated if it is inadvertently swallowed. The sodium content should be considered for patients receiving a low-sodium diet.[9] Other saliva substitutes include Saliva Substitute™ (Roxane), Moi-Stir® and Moi-Stir© Swabsticks (Kingswood), Entertainer's Secret® (KLI Corp), Salivart® (Gebauer), MouthKote® (Parnell) and Numoisyn™ (Align).[19]

Gelclair® (distributed by EKR Therapeutics), is a bioadherent oral gel available for use in the treatment of oral mucositis. It is a viscous oral gel (prescription medical device) that mechanically provides pain relief by adhering to the mucosal surface of the mouth. The main ingredients include purified water, maltodextrin, propylene glycol, polyvinylpyrrolidone, hyaluronic acid and glycyrrhetinic acid.[16] It is available in a package of 15 packets. Patients should be instructed to pour the entire contents

of a single-dose Gelclair® packet into a glass and add 1 tablespoon of water (15 mL). The mixture should be stirred and used immediately. Patients should:

1. Rinse the gel around the mouth for at least 1 minute to thoroughly coat the tongue, roof of the mouth, throat and buccal surfaces.
2. Gargle and spit out.
3. Wait at least 1 hour before eating or drinking.

Predicting, preventing to the limited extent possible and adequately responding to the onset of oral mucositis is a multifactorial, complex, ongoing clinical issue. As Kwong states,[20] it is unlikely that a single agent will be sufficient to both prevent the occurrence of mucositis as well as accelerate oral mucosa recovery. A stage-based treatment approach should be considered, whereby different interventions can be targeted at different stages of mucosal injury.

Table 1 Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) Clinical Practice Guidelines for the Prevention and Treatment of Mucositis Levels of Evidence.

Level of Evidence	Source of Evidence
I	Metaanalysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)
II	At least 1 well-designed experimental study; randomized trials with high false-positive, high false-negative errors or both (low power)
III	Well-designed, quasiexperimental studies, such as nonrandomized, controlled, single-group, pretest-posttest comparison, cohort, time or matched case-control series
IV	Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Case reports and clinical examples
Grade of Recommendation	
A	Evidence of Type I or consistent findings from multiple studies of Type II, III or IV
B	Evidence of Type II, III or IV and findings are generally consistent
C	Evidence of Type II, III or IV, but inconsistent findings
D	Little or no systematic empiric evidence
Guideline Classification/Hierarchy	
Recommendation	A recommendation is reserved for guidelines that are based on Level I or Level II evidence
Suggestion	A suggestion is used for guidelines that are based on Level III, Level IV and Level V evidence; this implies panel consensus on the interpretation of this evidence
No guideline possible	No guideline possible is used when there is insufficient evidence on which to base a guideline; this conclusion implies that 1) there is little or no evidence regarding the practice in question or 2) that the panel lacks a consensus on the interpretation of existing evidence

Table 2 Significant Revisions to the MASCC/ISOO Clinical Practice Guidelines for the Prevention and Treatment of Mucositis (Oral Mucositis Revisions Only).

Item	Recommendations
Basic oral care and good clinical practice principles	· Multidisciplinary development and evaluation of oral care protocols and patient and staff education in using such protocols to reduce the severity of oral mucositis from chemotherapy and/or radiation therapy · Use and regular replacement of a soft-bristle toothbrush with regular flossing, rinsing and moisturizing · Use validated tools to regularly assess oral pain and oral cavity health · Dental examinations prior to and throughout treatment and follow-up
Radiotherapy: Prevention and/or treatment	· Do not use antimicrobial lozenges for the prevention of radiation-induced oral mucositis (Level II, Grade B) · Do not use sucralfate for the treatment of radiation-induced oral mucositis (Level II, Grade A)
High-dose chemotherapy with or without total body irradiation plus HSCT: Prevention	· In patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation, use KGF-1 (palifermin) in a dose of 60 mcg/kg/ day for 3 days prior to conditioning treatment and for 3 days posttransplantation for the prevention of oral mucositis (Level I, Grade A) · Use cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan (Level II, Grade A) · Do not use GM-CSF mouthwashes for the prevention of oral mucositis in patients undergoing HSCT (Level II, Grade C)

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Nutritional Considerations in the Patient with Oral Mucositis

Mention the word "nutrition" in the context of cancer and you have a topic almost as complicated as the chemotherapeutic regimens employed in the treatment of the disease. The discussion could refer to a variety of aspects of care, ranging from cancer prevention diets, to dietary supplements or enteral

and parenteral nutrition, among others. For purposes of this review, we will consider the patient who has been diagnosed with cancer and will follow nutritional considerations through diagnosis, treatment and follow-up.

The most common oral complications related to cancer therapies are pain, mucositis, infection, salivary gland dysfunction and taste dysfunction. These complications can lead to dehydration and malnutrition.[1] Signs may include rapid weight loss, dehydration, nutritional stomatitis and secondary oral infection, such as candidiasis.[2] Sonis et al.[3] in a study of 92 HSCT patients, determined the extent and severity of oral mucositis is significantly correlated with days of injectable narcotics, TPN and injectable antibiotics; risk of significant infection; hospital days; hospital charges and mortality. The authors also found total hospital charges were almost $43,000 higher among patients with ulceration than without.

In a retrospective set of personal interviews with patients who had received radiotherapy for head and neck cancers, Rose-Ped et al.[4] found that 88% of patients interviewed could not eat or drink, or did so with extreme difficulty at some point in their course of therapy. Eighty-three percent reported significant weight loss, ranging from 12 to 79 pounds (mean 29 pounds). Weight loss led to gastric tube insertion for 29% of patients.

Nutrition intervention may include nutrition screening, assessment, evaluation, education and treatment for many symptom-management–related issues in cancer patients. Early intervention with specific nutritional therapy may slow or reverse the processes leading to malnutrition in patients with cancer. Nutritional assessment is a comprehensive process intended to prevent or treat malnutrition in individuals at risk. This requires a comprehensive nutritional assessment at the time of the cancer diagnosis and at regular, determined intervals thereafter.[5]

There are 2 phases to nutritional assessment: screening (usually conducted by nursing) and assessment (usually conducted by a registered dietitian). The screening phase of nutritional assessment is intended to identify those individuals who are at risk for malnutrition or who are already malnourished. While there are a number of institution-specific screening tools available,[6] the tool familiar to many clinicians is the Patient Generated Subjective Global Assessment. The assessment phase is intended to determine the nutritional status of the patient. Subjective data used for this purpose include medical, nutritional, social and medication histories. Objective data include physical examination, anthropometric measurements and laboratory values.[5,6,7,8] Based on these data, a patient may be classified as low, moderate or high risk for malnutrition. Because no one nutritional assessment tool is sufficient to diagnose malnutrition,[6] one can consider a 5% weight loss within 1 month, a 10% weight loss in 6 months or continued weight loss as indicative of a moderate risk for malnutrition; greater weight loss can indicate a high risk for malnutrition.[7,9,10,11]

Traditionally, nutrition assessment consists of historical data, biochemical data and anthropometric data. The history component includes pertinent medical history, diet history and weight history. Biochemical data can include a variety of information, such as visceral protein indices (albumin, transferrin, pre-albumin), total lymphocyte count, hemoglobin, hematocrit, nitrogen balance studies, lipid profiles and blood glucose. Indices of visceral protein are often used in nutrition assessments; although, institutions vary as to which indices are used.

To define the extent and depth of the nutritional problem, if any, a patient must be appropriately screened and assessed. Table 1 lists suggestions for performing a complete, accurate assessment:

Table 1[12]

Parameter	Suggested Action
Use the appropriate screening/assessment tool.	· Establish a risk category. · Flag nutritional deficits and problems. · Produce a nutrition care plan and nutrient goals.
Food intolerance, aversions and changes in taste perception.	Define food intolerance, food aversions and changes in taste perception or preferences.
Appetite, satiety and other factors affecting food intake or tolerance.	Assess the amount of decreased appetite; early satiety; head, neck or gastrointestinal discomfort or symptoms affecting food intake or tolerance.
Assess weight changes.	· Significant weight loss may be experienced by 45% or more of all adult hospitalized cancer patients. · Assess pre-illness adult weight status, prior 6-month weight patterns, admission weight and current weight. · Review influences, such as edema, ascites and hydration status.
Assess medical status.	· Check for other clinical conditions, such as diabetes, heart disease, hypertension and or renal disease. · Obtain a list of all medications being taken. · Obtain a history of previous therapy, treatments or medical management.
Evaluate nondietary factors affecting nutritional status.	· Age – if the patient is young or elderly, screening and assessment parameters should be age appropriate. Body composition, weight and metabolic rate should be evaluated accordingly, using appropriate tables and algorithms. · Functional status – mobility, dexterity, visual acuity, range of motion, mental status, pain status should be evaluated. · Access resources to determine if adequate means are available to the patient to obtain, prepare and ingest food. · Financial, psychological and social conditions that may influence eating. Acquire laboratory parameters from the medical record that will provide insight on the clinical status of the patient.
Assess the effect of the disease process on nutritional status.	· Tumors within the GI tract may block the passage of food. · Tumors outside the GI tract may press on or block organs or parts of the GI tract. · Systemic effects of the tumor may lead to early satiety or aversions to certain foods.

Anthropometric data include measurements of weight and height as well as BMI. Although the previously mentioned data are objective, a good clinician always uses subjective judgment to complete an assessment.

Nutrition alterations along with aggressive pain management can help to maximize the patient's tolerance of oral intake during episodes of mucositis. Suggestions for patients include:

- Avoid fruits and juices high in acid (such as orange, lime, lemon, grape fruit, tomato, pineapple)
- Avoid salty foods
- Avoid spicy foods
- Avoid alcohol
- Eat and drink foods at room temperature
- Eat soft foods, including foods that can be mashed with a fork or foods that have been blended
- Avoid rough-textured foods, such as raw vegetables, crackers, granola and popcorn
- If mucositis is severe, patients may have to be fed with either enteral or parenteral nutrition

Topical medications may be beneficial for mild mouth or throat pain and discomfort. Moderate to severe mucositis or systemic pain may be better managed using a narcotic patient-controlled analgesic 10 to 15 minutes prior to eating.[13]

The ability to maintain adequate oral intake during treatment relies on the involved oral tissues and presence of oropharyngeal mucositis from radiation or chemoradiation. Although many patients receiving radiation alone to the oral cavity, nasopharynx or neck may be able to tolerate soft foods early in treatment, most patients must transition to liquid diets using liquid nutritional supplements or have an enteral feeding tube inserted. Almost all patients receiving chemoradiation to the head and neck area, become fully dependent on enteral nutrition after 3 to 4 weeks of therapy. Mucositis and resulting odynophagia and dysgeusia make eating and secretion management difficult. Gastrostomy tube placement prior to beginning radiation treatment has been shown to prevent treatment interruption and weight loss.[14] Early nutrition intervention is key to alleviating many of the side effects of chemotherapy

Table 2

Safety Concern	Dietary Supplements
Potential interaction with certain antineoplastic chemotherapy	Antioxidants (eg, beta-carotene, alpha-tocopherol, coenzyme Q10, others)
Coagulation effects – procoagulation	Phytoestrogens, PC-SPES
Coagulation effects – anticoagulation	Garlic, ginkgo, saw palmetto, others
Interactions with warfarin	Coenzyme Q10, St. John's Wort, Danshen, Dong quai, others
Immune system stimulation	Melatonin, echinacea, Panax ginseng, coriolus mushroom, others
Immunosuppression	Long-term use of echinacea, green tea, ginger
Drug interactions with immunosuppressant medications	Echinacea, St. John's Wort, garlic, others
Agents with hormonal properties	Alfalfa, black cohosh, chasteberry, others
Supplements with known safety issues	Kava kava, ma huang
Supplements with known drug interactions	Grapefruit juice, St. John's Wort

and radiation therapy.

Additionally, the use of complementary medicines or dietary supplements must be evaluated in the course of determining treatment. Michaud and colleagues recently published an extensive, 2-part review of dietary supplements in patients with cancer care.[15,16] They reviewed complementary (therapies used in conjunction with conventional approaches) and alternative (therapies used instead of conventional therapies) medicine use as it relates to patient safety across a number of safety variables. Refer to Table 2 for a brief review of these variables and a sample of dietary supplements that may contribute to the safety concern.

The authors conclude that, while the body of literature related to the use of complementary and alternative medicine is growing, the extrapolation and application of this information to patient care remain complex. Continual review of conclusive evidence of efficacy/inefficacy and safety and open communication with patients are encouraged.

Nutritional considerations in the patient with oral mucositis are clearly complex and multifaceted, requiring a multidisciplinary approach. As evidenced by the above discussion, pharmacists are an excellent source of information concerning complementary and alternative therapies. Zogbaum et al.[17], in a chart review of 125 head and neck cancer patients treated with radiation therapy, concluded that appropriate nutrition assessment, monitoring and medical nutrition therapy can support an uninterrupted course of radiation therapy, which could improve the ability to treat the cancer. Molassiotis[18] advises us that nurses need to pay more attention to issues of nutrition in cancer patients throughout their course of cancer illness. Also, Borbasi et al.[19] remind us that, in addition to providing pharmacologic pain relief and routine mouth care, nurses provide encouragement and listen to patients' wishes, ameliorate symptoms when mucositis is at its peak and provide alternate forms of medication, all of which increase patients' sense of control. Finally, Sonis et al.[20] states that strong multiprofessional and interdisciplinary collaboration has resulted in marked advances in the improvement of psychometric and utilization components of mucositis scales.

However, we still have miles to go in maximizing the management of oral mucositis. Nurses, nurse practitioners, physicians, physician assistants, dentists, dental hygienists, nutritionists, pharmacists and others have distinct yet intertwined roles in effectively managing the complex myriad of issues faced by the patient with cancer and its resultant comorbidities. All professionals are encouraged to share the thinking, science and understanding that lead to breakthroughs in therapy.

Nutritional considerations in the patient with oral mucositis are clearly complex and multifaceted, requiring a multidisciplinary approach.

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Xerostomia

John Inzerillo, MD

Xerostomia, or dry mouth, results from decreased or absent saliva production secondary to a disease such as cancer or Sjögren's Syndrome. Patients with cancer develop xerostomia as a consequence of the effects of chemotherapy and/or radiation therapy on the salivary glands. It is the probable autoimmune-induced inflammation and infiltration of the exocrine glands (especially the salivary and lacrimal glands) by lymphocytes and plasma cells that causes xerostomia in Sjögren's Syndrome.[1]

Radiotherapy to the head and neck region causes acute and chronic xerostomia. As reported by Brizel et al., grade ≥ 2 (symptomatic and significant oral intake alteration) acute and chronic xerostomia occurred in 78% and 57% of previously untreated patients with head and neck cancer. They were given once-daily radiation doses to a total of 50 to 70 Gy.[2] In patients who undergo HSCT, the risk of acute and chronic GVHD (30%-50% and 30% respectively) and consequent xerostomia is a major concern. Many HSCT conditioning regimens include the administration of total body irradiation, which causes significant xerostomia. Chemotherapy agents in these regimens, such as high-dose cyclophosphamide, busulfan and melphalan, also will individually result in xerostomia.[3]

The CTCAE defines xerostomia using the following grades:

Grade 1 – symptomatic (dry and thick saliva) without significant dietary alteration: unstimulated saliva flow > 0.2 mL/min

Grade 2 – symptomatic and significant oral intake alteration (ie copious water, other lubricants, diet limited to purees and/or soft moist foods), unstimulated saliva 0.1 to 0.2 mL/min

Grade 3 – symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings or TPN indicated, unstimulated saliva < 0.1 mL/min[4]

In a study reported by Roh J-L et al., QOL questionnaires suggested that decreased salivary function resulted in speech and eating problems and subsequently reduced social contact or activity.[5] Unfortunately, all patients receiving radiation to the head and neck region will experience varying degrees of dysphagia, and up to one half may have significant dysphagia.[6] A study by Stenson et al. demonstrated that 40% of head and neck cancer patients had some and 4% had moderate to severe dysphagia at presentation. Larynx and hypopharynx tumors caused worse function than those in the oral cavity and oropharynx.[7] These numbers are most likely on the low side of what is seen in clinical practice, as Rosenthal et al. report that dysphagia and the resultant aspiration it can cause are under-reported and underappreciated consequences of head and neck cancer treatment.[8]

Xerostomia can interfere with taste perception. It occurs secondary to chemotherapy-or radiation therapy-induced damage to the taste buds. A secondary mechanism that explains the appearance of dysgeusia is the presence of chemotherapy in the saliva. Altered taste can be defined as 1) hypoageusia, 2) ageusia and 3) dysgeusia (distortion of normal taste). Anywhere from 36% to 71% of cancer patients report a distressing change in taste, most commonly dysgeusia. The chemotherapeutic agents associated with dysgeusia include cyclophosphamide, carboplatin, cisplatin, gemcitibine, interferon-gamma, lupron, levamisole, tamoxifen and VP-16. The change in taste can persist for days to months after chemotherapy. Dysgeusia is also associated with emesis.

Radiation therapy will also lead to dysgeusia with maximum gustatory loss seen at doses between 50 to 60 Gy. As stated above, radiation will affect the flow and composition of saliva and these changes predispose the buccal mucosa to bacterial and fungal overgrowth.[9] HSV reactivation can also be seen after chemotherapy, although not as frequently as fungal infections.

Other infections associated with xerostomia include oral and esophageal candidiasis, most commonly with *Candida albicans*. When *Candida* involves either of these areas, resultant weight loss and cachexia can occur secondary to associated dysphagia. It should be noted that *Candida* species itself is not involved in the mucositis process, but it can lead to systemic infection in the presence of xerostomia and ulceration.[11] In other words, bacterial, viral and fungal infections can become established in the presence of oral mucositis. It is in the face of severe immunosuppression that these infections can become systemic. A study by Ramirez-Amador et al.[12] found when salivary glands are included in the radiation field, xerostomia occurs and there is a progressive increase in oral *Candida* colonization. At baseline, 43% of patients had positive cultures while at the completion of radiation therapy 62% had positive cultures. As such, candidiasis is the most common infection in the oral cavity during or

shortly after radiation therapy.

Xerostomia of any etiology will cause a shift in oral microflora toward cariogenic bacteria, thus leading to a higher incidence of dental caries. Reduced salivary flow and altered saliva composition (buffer capacity, pH and immunoproteins – specifically the loss of the protective function of IgA) will lead to an increased incidence of dental caries and periodontal infections. An increase in *Streptococcus mutans* and *Lactobacillus* species, along with the changes in salivary composition, will contribute to poor dental health and halitosis.[10]

The symptoms associated with xerostomia are many and include dry mouth and dry tongue, both of which may be fissured and painful. In an effort to keep the mucous membranes moist, patients may drink more water during the daytime and experience polyuria and polydipsia. The lips may also be dry, cracked, fissured and painful. Speech, swallowing and chewing will

be hampered secondary to the decrease or absence of saliva. If prosthetic appliances are used, patients will develop intolerance to them as saliva is an effective lubricant to the denture-mucosal interface. With decreased saliva, friction between the appliance and the gingiva is increased, and traumatic injury is more likely to occur. Weight loss will occur because of dysgeusia, dysphagia and/or any one of the infectious processes mentioned above.[10] Patients who have concomitant fluid loss through vomiting and/or diarrhea, as do most patients undergoing high-dose chemotherapy and irradiation to the gastrointestinal tract, are placed at significant risk.

> The best management option for xerostomia is anticipation and recognition of its onset.

The best management option for xerostomia is anticipation and recognition of its onset. For this reason, many agents have been utilized in an effort to prevent radiation-induced xerostomia and mucositis. The following section will discuss what patients can do for self-care to manage xerostomia. Additionally, it is important for health care professionals to work with patients and their families to educate them regarding effective dental care and the pharmaceutical options available.

A daily mouth exam should be undertaken to identify red, white or dark patches and to identify tooth decay. Plaque removal and treatment of dental caries are essential. Brushing with a frequently changed, soft toothbrush and flossing daily will help prevent caries. A low-abrasive toothpaste should be used. Sodium fluoride rinses can be used and should be held in the mouth for at least 1 minute before expectorating. If the patient is producing saliva, sialogogues should be used. Dentures should not be worn overnight. Sugary or acidic foods and beverages should be avoided as should dry, spicy, astringent, excessively hot or cold consumables. Smoking and alcohol consumption should be avoided.

Artificial saliva and saliva substitutes can be used to replace moisture and provide lubrication for the mouth. A list of commercially available products follows:

- Caphosol (Cytogen) advanced calcium/phosphate electrolyte solution.
- Carboxymethyl or hydroxyethylcellulose solutions:
  - Entertainer's Secret (KLI Corp) spray
  - Glandosane (Kenwood/Bradley) spray
  - Moi-Stir (Kingswood Labs) spray
  - Moi-Stir Oral Swabsticks (Kingswood Labs) swabs
  - Optimoist (Colgate-Palmolive) spray
  - Saliva Substitute (Roxane Labs) liquid
  - Salivart (Gebauer) preservative-free aerosol
  - Salix (Scandinavian Natural Health & Beauty) tablets
  - V. A. Oralube (Oral Dis. Res. Lab) sodium-free; liquid
  - Xero-Lube Artificial Saliva (Scherer) sodium-free; spray
- Mucopolysaccharide solutions
- MouthKote (Parnell) spray

As discussed in the "Oral Mucositis: Treatment Action Plans" article, Caphosol is now available for use in patients with dryness of the mouth or throat (hyposalivation, xerostomia) regardless of the cause. Caphosol is comprised of 2 separately packaged aqueous solutions, a phosphate solution (Caphosol A) and a calcium solution (Caphosol B) which, when combined, form a solution supersaturated with both calcium and phosphate ions. It is designed in part to replace the normal ionic and pH balance in the oral cavity. Relief of dryness of the oral mucosa in patients with xerostomia, oral mucositis or hyposalivation is associated with pain relief. Patients should be instructed to avoid eating or drinking at least 15 minutes after use and to store the product at room temperature; refrigeration is not required. Importantly, there are no known interactions with Caphosol and drugs or other products.

In addition, SALAGEN (pilocarpine hydrochloride - MGI Pharma) is indicated for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck. Both SALAGEN and EVOXAC (cevimeline - Daiichi Pharmaceutical Co.) are indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome. Refer to the "Oral Mucositis: Treatment Action Plan" article for more information.

Antixerostomia dentifrices are also available that contain 3 salivary enzymes (lactoperoxidase, glucose oxidase and lysozyme) that activate intra-oral bacterial systems. They include the following products:[13]

- Biotene® Dry Mouth Toothpaste
- Biotene® Gentle Mouthwash
- Biotene® Dry Mouth Gum
- Oralbalance® Long-lasting Moisturizing Gel
- Biotene® Dry Mouth Kit

Xerostomia is one of the most common complaints that cancer patients experience, both in the acute and chronic setting. Attending to the associated symptomatology and following through with treatment is required to successfully manage this disabling condition.

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Interview: Oral Care in Patients with Oral Mucositis

Dr. Athena S. Papas is a dentist, professor of oral medicine, co-head of the Division of Geriatric Dentistry at the Tufts University School of Dental Medicine and researcher who specializes in the care of patients with xerostomia and oral mucositis. Dr. Papas' studies have tested a variety of oral care interventions, including saliva substitutes (eg, Caphosol), remineralizing toothpaste and fluoride and antibacterial varnishes. In fact, Dr. Papas sold the Caphosol patent for $1 to ensure swift patient access to this important therapy. Diversified Medical Education (DME) had the opportunity to speak with Dr. Papas about the importance of proactive oral mucositis management.

DME: Why is the management of oral mucositis such an important issue?
AP: Oncology treatments have immediate sequelae, such as severe inflammation of the oral mucosa, cellulitis, mucositis, dysphagia, dysguesia, severe weight loss, pain of varying intensity, long-term sequelae, such as salivary gland hypofunction, rampant caries, trismus (a tonic contraction of the muscles of mastication) and osteoradionecrosis (bone necrosis secondary to radiation). These complications lead to constant discomfort and can affect the patient's overall QOL. In chemotherapy and BMT patients, mucositis can provide an opportunity for oral microorganisms to cause systemic infections. These infections can increase morbidity and mortality. Salivary gland secretion diminishes markedly, or ceases altogether, in patients receiving more than 50 Gy of radiation to the head and neck. The extent of salivary damage depends on the field and dosage of radiation. A threshold of 26 Gy for salivary damage and 60 Gy for permanent damage has been suggested.

DME: What may be effective prevention and early treatment strategies for oral mucositis?
AP: It is important to work with the health care team to assess the best time for treatment. Dental evaluation is critical to assess for unrestorable, periodontally or endodontically involved teeth, sharp restorations or appliances.

Behavioral change may benefit any preventive program, but it is very difficult to change habits. Prescription-level fluoride is critical. Although gel trays are the gold standard, compliance is very poor. High-fluoride toothpastes and varnishes applied by health care professionals are easier to use and have better compliance. Remineralizing toothpastes, solutions, enamel care, Mentadent® Replenishing White (calcium/phoshate toothpaste and gels) and Caphosol (calcium/phosphate remineralizing rinse) should be used in conjunction with fluoride treatment. Also, sialogogues, xylitol gum and sonic tooth brushes stimulate saliva and help prevent dental caries.

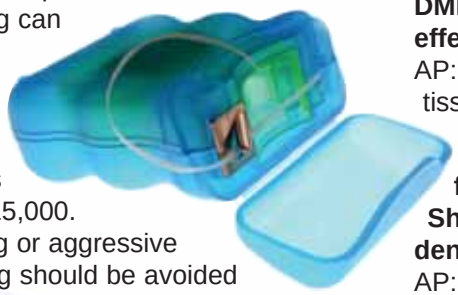
Currently, cryotherapy, palifermin, amifostine and Caphosol are the only clinically proven therapies for mucositis.

DME: Are there common treatment mistakes to avoid?
AP: Patients with dry mouth, xerostomia or oral mucositis are often encouraged to utilize hard candies to stimulate saliva production or otherwise moisten the oral cavity. However, candies can cause dental caries. Lemon candies specifically can exacerbate mucositis, caries and erosion. It is important to reduce exposure to sugar, add water to acidic drinks to dilute the acidity, drink beverages that have added calcium and discuss the importance of adequate saliva flow and function.

DME: What type of toothbrush should patients use?
AP: Patients should use an extra soft toothbrush. It should be noted that glycerin swabs can worsen mucositis. However, plain swabs can be used to clean out debris and necrotic tissue.

DME: You mentioned prescription-level fluoride treatment earlier. Is there value in over-the-counter fluoride or antiseptic rinses?
AP: Unfortunately, fluoride, chlorhexidine, benzydamine and triclosan rinses have not been found to be effective. Additionally, mouthwashes containing peroxide or alcohol and tartar control toothpastes can be irritating and should be avoided.

DME: What is your opinion regarding dental floss?
AP: Floss, when used correctly, is important to maintain gingival health. However, spontaneous bleeding can occur when the platelet count is below 15,000. Flossing or aggressive brushing should be avoided in that situation.



DME: What type of oral infection may be seen in oral mucositis patients and how might they be treated?
AP: Gram-negative bacteria can enter ulcerations in the oral mucosa. With loss of saliva, candidiasis is common and can worsen mucositis. Systemic fungal infections can be life-threatening. Antibiotics can reduce systemic microorganisms, but oral microorganisms persist and that can lead to systemic infection.

Candidiasis treatment varies and can include fluconazole 100 to 200 mg daily; Sporanox® 100 mg/10 mL liquid twice daily; Sporanox® 100 mg capsule twice daily; itraconazole oral suspension 10 mg/10mL; and intravenous

amphotericin B. Noxafil® is a newer agent that should be administered at a dose of 400 mg twice daily for the treatment of refractory invasive fungal infection. In patients with dysphagia, Noxafil should be administered at a dose of 200 mg 4 times daily. For the treatment of oropharyngeal candidiasis, Noxafil should be administered as a loading dose of 200 mg on the first day, then 100 mg once daily for 13 days. It should be taken with food.

DME: Are there any known long-term effects of mucositis?
AP: Mucositis eventually heals, but the tissue is changed.

DME: How should patients be followed after their treatment? Should they have more aggressive dental visits?
AP: Patients should be followed regularly, with dental visits every 3 months.

DME: When should an oncologist or oncology nurse refer a patient to a dentist?
AP: Dentists should be part of the oncology team. When the patient's laboratory values are appropriate, dental treatment can be rendered before the next chemotherapy treatment.

Importantly, all head and neck radiation therapy patients should be referred for a pretreatment evaluation to prevent osteoradionecrosis.

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A passing score of 70% or higher on the posttest awards the participant *2 AMA PRA Category 1 Credits™* or two (2) hours of continuing nursing education (CNE) credit or two contact hours (.2 CEU) of continuing pharmacy education (CPE) credits. To claim continuing education credit, individuals must complete the self-study activity, posttest and evaluation and either mail an answer sheet, postmarked by September 9, 2008 or access www.CECentral.com/getcredit and enter code XEN08060 to take the test online. There is no charge to the participant for completing the posttest and receiving continuing education credit.

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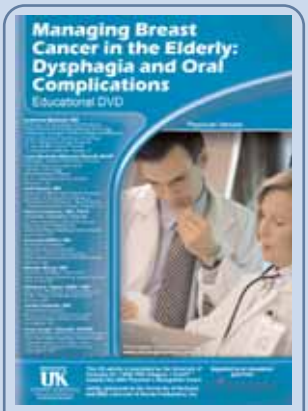
Managing Breast Cancer in the Elderly: Dysphagia and Oral Complications

Pharmacy/Nursing Video/DVD

Nursing Newsletter



Physician Video/DVD

Breast cancer treatment in the elderly is a management challenge. Of the approximately 200,000 new breast cancer cases diagnosed each year in the United States, approximately 50% occur in women over age 65. Approximately 60% of the 40,000 annual breast cancer deaths occur in women over age 65.

Current and available treatment modalities include localized therapies such as surgery and radiation as well as systemic therapies such as chemotherapy and hormonal therapy. Approximately 75% of postmenopausal breast cancer patients have estrogen-dependent tumors. Study data on women who started tamoxifen indicate that one-third failed to complete the recommended 5-year course, with the highest rates of failure among the elderly. Failure to adhere to tamoxifen therapy has been attributed to side effects and polypharmacy. Other factors that have been attributed to adherence failure are dysphagia, economic considerations, cognitive impairment and the patient's own belief that they have "lived long enough."

Medication adherence is an important part of therapeutic outcome. In the elderly, dysphagia and other oral complications, such as xerostomia and oral mucositis, may be common and can affect medication adherence, since the ability to chew and swallow both food and pills may be compromised. These programs examine the causes and care of patients with dysphagia and other common oral complications. They also look at treatment options, including soluble forms of hormonal therapy, which may positively affect patient adherence and, ultimately, patient outcomes.

UK UNIVERSITY OF KENTUCKY
Pharmacy and Medicine Continuing Education

This program is supported by an educational grant from
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These CE activities are accredited by the University of Kentucky for one contact hour (.1 CEU) of continuing pharmacy education (CPE) credit, one (1) hour of continuing nursing education (CNE) credit or *1 AMA PRA Category 1 Credit™* towards the AMA Physician's Recognition Award.

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