Oral mucositis

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Oral mucositis remains one of the most common and troubling side effects of standard chemoradiation regimens used for the treatment of head and neck cancer. Virtually all patients who receive cumulative radiation doses of more than 30 Gy that includes oral mucosal fields will develop the condition. Not only does mucositis cause extreme discomfort, often necessitating opioid analgesia, but it is also associated with increased use of health resources and cost of treatment. The incremental cost of mucositis in patients with head and neck cancer is more than $17 000 (US). Much has been learned about the pathobiology that underlies the condition. The departure from the historical paradigm of direct cell death as being the primary cause for mucosal injury in favor of a more comprehensive view of the impact of chemoradiation on all the cells of the mucosa, has resulted in a picture of mucositis pathogenesis, which is biologically broad based. Although there are currently few treatment options for oral mucositis at the moment, the recognition that its underlying biology is complex has provided a range of treatment options that are currently being developed. *Anti-Cancer Drugs* 22:607–612 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Oral mucositis is among the most common tissue toxicities associated with radiation therapy used for the treatment of cancers of the head and neck. It results in the development of diffuse ulcerative lesions of the movable mucosa of the mouth and oropharynx, with consequent pain of such severity as to require opioid-level analgesics [1]. Patients consistently report that it is the most bothersome side effect of the treatment that they experience.

Virtually all patients who receive radiation therapy with or without concomitant chemotherapy will develop ulcerative mucositis. Severe mucositis is reported to occur with a frequency exceeding 90% for patients being treated for cancers of the mouth and oropharynx [2]. Among patients with cancers of the hypopharynx or larynx, the frequency of mucositis is somewhat less, approximately 65%. In addition to the symptomatic toll incurred by mucositis, it also significantly alters the quality of life of patients and the use of health resources. Patients with mucositis cannot tolerate normal diets and often rely on gastrostomy feedings for nutritional supplementation. In addition, patients with mucositis have more unplanned office visits and emergency room visits, usually for pain management and hydration, than do patients without the condition, and are hospitalized with higher frequency. As a result, the incremental cost of oral mucositis in the patient population with head and neck cancer (HNC) is more than $17 000 [3].

Despite its frequency and clinical and economic impact, the recommended treatment for mucositis is largely palliative. A single agent, palifermin, has been approved as a mucositis intervention and its use is limited to patients with hematological malignancies undergoing stem cell transplant. Although benzydamine is approved in Europe, its efficacy seems to be limited to patients receiving radiation-only regimens. Its efficacy wanes when concomitant chemoradiation regimens are used [4].

Clinical course of mucositis

The clinical course of mucositis is relatively predictable in patients receiving fractionated radiation regimens for HNCs in which the typical radiation fraction is 2 Gy per day for 5 days per week to a total cumulative dose of 60–70 Gy. Concomitant chemotherapy using standard weekly or triweekly cisplatin seems to increase the severity of mucositis, but does not influence the course of the condition.

By the end of the first week of treatment (cumulative radiation therapy dose of 10 Gy), erythema of the mucosa is noticeable and patients complain of symptoms analogous to a diffuse food burn. Symptomatic relief at this stage is usually achievable with topical palliative agents or NSAIDs. Early ulcerative changes are often seen by the end of the second week of treatment and are accompanied by an increase in symptoms. Discomfort at this stage may necessitate an increase in analgesic intensity and patients may have less tolerance for a standard diet. At cumulative radiation doses of 30 Gy or more, diffuse mucosal ulceration is common. Lesions typically involve the movable mucosa of the cheeks, lips, ventral and lateral tongue, floor of the mouth, and soft palate. It is not usual for mucositis to affect the more heavily keratinized mucosa of the dorsal tongue, gingiva,

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or the hard palate. Lesions of these sites are often of an infectious etiology. The ulcerative lesions associated with severe mucositis are irregular, may be associated with peripheral areas of erythema, and are often covered by a pseudomembrane made up of fibrinous exudates and dead cells. Mucositis at this stage is extremely uncomfortable. Although there are no sentimental sites for lesions, it seems that those involving the floor of mouth, lateral tongue, and the soft palate are the most symptomatic. Patients cannot eat normally; many require gastrostomy tube feedings and some require breaks in treatment. Ulcerative lesions usually persist for 2–4 weeks after the completion of radiation when they resolve spontaneously.

Mucositis assessment

The lack of a uniform reported scale to describe mucositis has been an impediment to consistency in reporting the course and the severity of the condition. Almost two dozen scales are currently in use. These vary from global assessment tools to hospital-specific nursing management instruments [4].

The WHO and National Cancer Institute (NCI) scales are the most commonly used. These differ in the criteria used to assess mucositis severity. The WHO scale relies on a combination of clinician-based observations (erythema and ulceration) in conjunction with a measurement of the impact of mucositis on patient function as measured by the ability to eat. Ease of use is the strength of the WHO scale. Ulcerations are assessed as being either absent or present. Size is not a consideration. A potential confounder of the WHO scale is based on the need for the evaluator to determine the patient's dietary intake ability. The difference in grade between a patient with an ulcer who can eat solids (WHO 2) and one who cannot tolerate anything by mouth (WHO 4) has significant implications. It is incumbent on the evaluator to assure that patient's food tolerances are because of mucositis rather than another cause, such as nausea.

In contrast, the NCI-common toxicity criteria has two different scales to evaluate mucositis. One is based on a clinician-based assessment of tissue changes (erythema and the extent of ulceration and pseudomembrane formation). The other is based on patient function. The former scale is the one that is most used. In using the NCI scale, the examiner must provide an accurate assessment of the extent of ulcerative changes.

It has been observed that the NCI scale scores based on clinical observation of lesions tend to be lower than those reported using WHO criteria. This is likely the consequence of ulcerative mucositis on function as measured by the score. For example, although a 1 cm ulcer of the soft palate would be scored as 2 on the NCI scale, it might be so symptomatic as to prevent the patient from eating normally and to limit intake to fluids (WHO 3) or even nothing by mouth (WHO 4).

Mucositis pathobiology

For years, conventional thinking around the pathogenesis of mucositis was based on the premise that cytotoxic therapy in the form of radiation or chemotherapy nonspecifically targeted the rapidly dividing cells of the oral basal epithelium. The idea was that the resulting clonogenic cell death meant that epithelial renewal ceased and the tissue became atrophic and ultimately ulcerated. Over the past decade, this concept has been replaced by the realization that mucositis (and other regimen-related tissue injury) is not only from the consequence of direct cell injury but also, more significantly, from the consequences of a series of complex biological events, many arising in the cells and tissues of the submucosa [5]. The intricacy of this process is reflected by the finding of 14 canonical pathways identified by genomic analysis of peripheral blood cells from patients with HNC, which were related to the development of mucositis [6]. To illustrate the biological sequence of mucositis development, a five-phase model has been described [7]. Clearly, administration of fractionated radiation results in an overlap of the cellular events, which culminate in tissue injury. Nevertheless, the model provides a basic structure for understanding the process and a basis for additional discovery and investigation. It has also served as a delineation of potential pharmacological treatment targets and as a source of possible predictive biomarkers.

The first phase of mucositis is termed as initiation. Its primary feature is the development of reactive oxygen species (ROS) and consequent oxidative stress. That oxidative stress plays a role in the initiation of mucositis is borne out by a number of observations. First, ROS induce two important transcription factors, nuclear factor-κB (NF-κB) and STAT3, both of which provide the activation of genes that are associated with tissue-damage-mediating cytokines. The nrf2 pathway has also been observed to influence the degree of radiation-induced oxidative stress, and patients deficient in glutathione transferase activity are at an increased risk of developing mucositis [8].

The second component of the initiation phase involves the innate immune system of the host [9]. In addition, cells made apoptotic or necrotic as a consequence of radiation may release endogenous damage-associated pattern molecules that initiate toxicity in a manner reminiscent of danger-associated molecular pattern of the innate immune system. These molecules, called chemotherapy/radiation-associated molecular pattern, initiate a cascade of biological events, including the binding of chemotherapy/radiation-associated molecular pattern molecules to pathogen recognition receptors, which are located in epithelial and endothelial cells, and the activation of transcription factor mediators that play a role in mucosal injury.

This all leads to the second phase of mucositis, the primary damage response phase. Although the activity in

this phase precedes any visible clinical changes, it is extremely active. Even as direct cell death as a consequence of DNA strand breaks occurs, significant intercellular and intracellular signaling occur in the connective tissue, endothelium, and infiltrate of the submucosa. The consequences of this activity are directed toward the mucosal epithelium. ROS, chemotherapy, and radiation therapy all can activate a number of transcription factors of which NF-κB is probably the best studied. As a result, a number of significant genes are expressed, including those controlling the production of proinflammatory cytokines, endothelial growth factors, and cycloxoygenases. Simultaneously, the enzymes of the ceramide pathway, ceramide synthase, and sphingomyelinase are also activated. Finally, damage to connective tissue fibrin leads to the activation of matrix metalloproteinases. All of these culminate in apoptosis of cells of the basal epithelium.

Biological feedback occurs in the next phase, signal amplification. During this time, many of the mediators generated during the primary damage response provide positive feedback to result in a growing cascade of damaging mediators. As an example, NF-κB is stimulated by tumor necrosis factor to continue its downstream activity. The same proinflammatory cytokines can also stimulate the metalloproteinase pathway. Biological crosstalk between cells is well established. After the stimulus provided by radiation, pathway activation is intense.

Epithelial proliferation comes to a grinding halt in response to the apoptotic and necrotic chain of events elicited by chemotherapy and radiation. As a result, mucosal thinning begins, ultimately resulting in the fourth and most clinically significant phase of mucositis, ulceration. The ulceration that occurs in mucositis transcends the whole of the epithelium. Although infiltrating cells are relatively sparse during the early phases of mucositis, the ulcerative phase is characterized by a robust infiltrate within which macrophages, neutrophils, and mast cells are observed. Bacterial colonization is a common feature of mucositis ulcerations. Studies tracking the local bacterial load show a dramatic increase following, not preceding, ulcer formation. The colonizing bacteria are not quiescent. Rather, cell wall products released from the organisms penetrate the disrupted mucosa and stimulate infiltrating macrophages likely through innate immune system pathways to produce additional proinflammatory cytokines.

During the final phase of mucositis, healing occurs. Extracellular matrix signaling to the epithelium impacts proliferation, migration, and differentiation. Epithelialization occurs at the ulcer margins and healing is generally complete within 4 weeks after the final dose of radiation.

Risk factors

A number of factors influence a patient's risk of mucositis and these can be grouped into two general categories: those associated with the treatment and those associated with the patient. In the case of patients who receive standard chemoradiation regimens, which include fields in the mouth in which the total cumulative dose of radiation is expected to exceed 30 Gy, the risk of mucositis is virtually 100% as the tissue challenge is overwhelming. Unlike patients receiving lower cumulative doses or patients being treated with chemotherapy (as in induction therapy for HNC), the aggressiveness of the focal tissue challenge is so overwhelming as to largely preclude other risk factors. Nevertheless, although the incidence of ulcerative mucositis is uniform, the time of onset and peak mucosal injury may be influenced by patient-related variables.

For example, among a group of patients being treated for an intraoral tumor at the same site with the same chemoradiation regimen, the onset of ulcerative mucositis and the peak severity may vary. The behavior of mucositis may be governed by genes that differentially impact the pathways involved in the pathogenesis of the condition. Some examples already exist. Glutathione-S-transferases are important detoxification enzymes that reduce radiation-induced and chemotherapy-induced oxidative stress by neutralizing ROS. Two genes, GSTM1 and GSTT1, show common deletion polymorphisms that result in a lack of enzyme activity. Consequently, Hahn *et al.* [8] evaluated the impact of these deletion single nucleotide polymorphisms on toxicity and mucositis risk in patients undergoing stem cell transplant. They found that patients who had both single nucleotide polymorphisms had an almost two-fold increase ($P < 0.035$) of developing toxicity. In specific terms, the difference in the development of mucositis was 55% for patients not having the polymorphisms and 74% for those who did.

In a study that focused on radiation-induced dermatitis, Ambrosone *et al.* [10] reached similar conclusions following lumpectomy for breast cancer. They also studied polymorphisms associated with glutathione-S-transferase. In a study of approximately 500 patients, they found that individuals who had a genotype associated with low enzyme activity were at twice the risk of radiation-induced skin injury. Interestingly, the risk ratio described by Ambrosone *et al.* [10] is almost the same as noted by Hahn *et al.* [8].

The influence of the local oral environment on mucositis

The oral cavity is one of the most biologically complex environments in the body. It is the only place in which hard tissue (teeth) communicates with the external environment. It is continuously bathed in a unique fluid (saliva) and its resident microflora is dynamic. That overall mucosal health is not influenced in some way by local factors seems, therefore, unlikely. Yet, interventional strategies for mucositis that have targeted the microbiota or that stimulated salivary flow have been unsuccessful [11].

It is clear that mucositis is not an infectious disease. Both quantitative and qualitative temporal bacterial analyses show that mucosal injury precedes increases in bacterial load. Once ulcerations are present, significant secondary bacterial colonization does occur with consequent increases in bacterial numbers. The biological impact of these bacteria in potentially influencing the duration and the severity of mucositis has already been discussed above. Although not the topic of this study, it is worth mentioning that bacteria may play a more dynamic role in the development of chemotherapy-induced mucosal injury within the small intestine and this topic is an area of active research [12]. Nevertheless, clinical observations in which prophylactic antibiotics fail to attenuate the development of mucositis are not consistent with a significant role for bacteria in regimen-related toxicity. Clearly, further study is needed in this area and it would be of great value to study mucositis in a gnotobiotic animal model.

Similarly, studies involving the role of oral fungi or viruses (particularly herpes simplex virus-1) have failed to support a hypothesis that either of these organisms play a primary role in the etiology of oral mucositis [13–15].

The role of saliva in the development of mucositis has been the topic of significant study. Certainly, saliva is more than a wetting agent. Its contents include antibodies, enzymes, and biologically active substances such as trefoil factor, a compound that has been suggested to be of therapeutic benefit in the treatment of mucositis. Furthermore, xerostomia is virtually a uniform side effect of radiation therapy, most significantly, when the parotid is included in the radiation field. Despite this, numerous interventional approaches aimed at increasing salivary flow have failed to modify the course or severity of oral mucositis [16].

Current and future treatment options

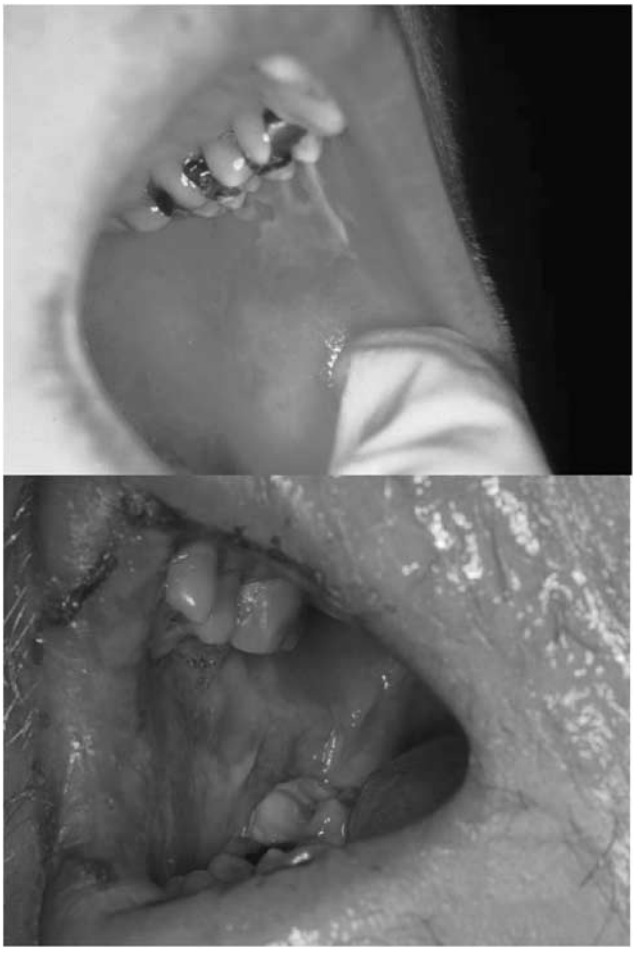
Despite its long history and its impact on patients, there are currently no effective options for the prevention or treatment of mucositis in patients receiving chemoradiation therapy for HNC.

Palifermin (keratinocyte growth factor 1) has approval as a mucositis intervention in patients receiving conditioning regimens before stem cell transplants for the treatment of hematological malignancies. Although palifermin is not used in patients with solid tumors, its approval is significant as it showed that a mechanistically based treatment approach could be successful. Palifermin is biologically pleotropic. Although it stimulates epithelial proliferation, its mucositis effects are largely likely because of its action on the nrf2 pathway, its ability to attenuate proinflammatory cytokine levels and stimulate anti-inflammatory cytokines, and its cytoprotective effects. The fact that an agent that targets the biological pathways involved in the pathogenesis of mucositis is efficaciously opens the door to other molecules with similar types of function [17].

The only topical agent that has shown efficacy in prospective, blinded, placebo-controlled, randomized trials for radiation-induced mucositis is benzydamine [4]. It seems likely that benzydamine, a nonsteroidal anti-inflammatory compound, gains its activity by modulating some of the mediators of injury. Benzydamine is approved for use in Europe, Canada, and South America, but not in the USA. It does not seem to be efficacious in treating mucositis induced by concomitant chemoradiation regimens.

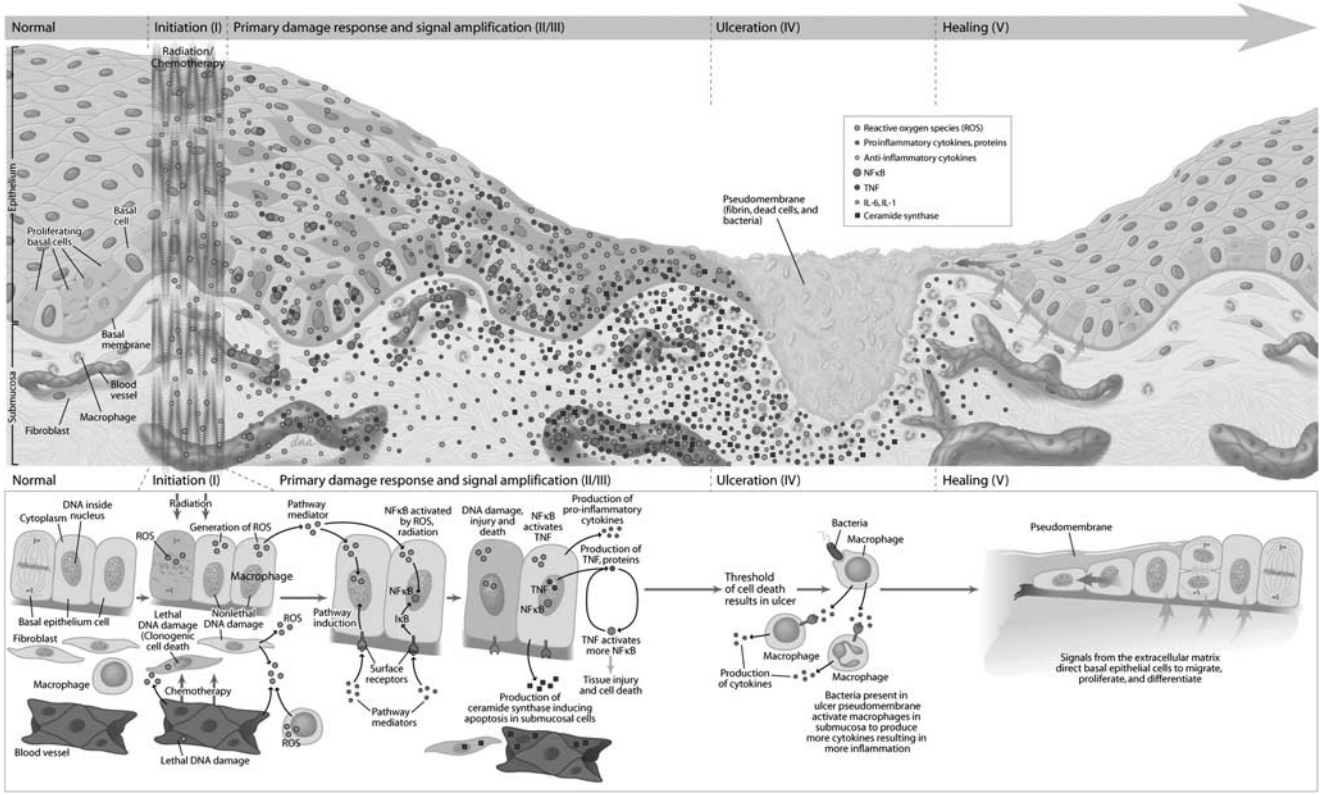
At least three compounds have gained approval as devices for the treatment of oral mucositis. These include Gelclair, Mugard, and Caphosol. Gelclair and Mugard purportedly function as coating barriers that palliate mucositis pain. Caphosol was originally released as a solution to provide remineralization of teeth in patients with xerostomic conditions, such as Sjogren's syndrome. There are anecdotal data to support the benefits of all three agents, but there

Fig. 1



Clinical features of mucositis. Ulceration is present on the patient's cheek in the bottom panel. Erythema and psuedomembrane formation are visible in the top panel.

Fig. 2



A multiple mechanism model for the pathobiology of mucositis. The pathobiology of mucositis as a five-stage process. The key biological processes associated with the pathogenesis of oral mucositis can be arbitrarily divided into five stages: initiation, primary damage response (messaging and signaling), amplification, ulceration, and healing. Reproduced with permission [22]. IL, interleukin; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; TNF, tumor necrosis factor.

are no blinded, randomized data to support their use in patients receiving conventional regimens for HNC. Magic mouthwashes are often recommended for patients at risk of mucositis. There is no standard formulation for these solutions. Most are unique to the institutions in which they were developed and typically contain a vehicle (Maalox, milk of magnesia, Kaopectate), a topical anesthetic such as Benadryl or lidocaine, and a variety of assorted compounds such as antifungals and topical steroids. When tested in the standard clinical trial format, these solutions have, for the most part, failed to be more beneficial than saline.

Oral mucositis remains a significant unmet clinical need, which impacts a large group of patients. Consequently, it has gained the attention of the pharmaceutical and the biotechnology industry and is actively being pursued. A range of compounds is currently in the clinical development pipeline [18–21]. Virtually all target the biological pathways associated with the pathogenesis of the condition. It seems likely that effective treatment options will become available in the next few years (Figs 1 and 2) [22].

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