

The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Abstract: Oral mucositis (OM) is a common, highly symptomatic complication of cancer therapy that affects patients' function, quality of life, and ability to tolerate treatment. In certain patients with cancer, OM is associated with increased mortality. Research on the management of OM is ongoing. Oral mucosal toxicities are also reported in targeted and immune checkpoint inhibitor therapies. The objective of this article is to present current knowledge about the epidemiology, pathogenesis, assessment, risk prediction, and current and developing intervention strategies for OM and other ulcerative mucosal toxicities caused by both conventional and evolving forms of cancer therapy.

Keywords: cancer, immune checkpoint inhibitors, immunotherapy, oral mucositis, stomatitis, targeted therapy, toxicity, ulcer

Introduction

Oral mucosal injury has been one of the most consistent side effects of anticancer drug and head and neck (H&N) radiation regimens. Damage to the oral mucosa, termed oral mucositis (OM), results in lesions that are so painful as to be refractory to even aggressive analgesic management. In severe OM (SOM), the patient suffers from oral ulcers, causing extreme pain that prevents oral intake. Consequently, SOM interferes with patients' ability to tolerate optimal treatment regimens, increases the risk of local and systemic infection, and adds significantly to health care resource use and cost. Furthermore, OM is associated with increased mortality in patients undergoing hematopoietic cell transplantation (HCT) (also known as hematopoietic stem cell transplantation).¹ Although OM traditionally is associated with cytotoxic forms of treatment, newer manifestations of the condition are seen with developing therapies, such as targeted and immunologically based agents.

Despite its clinically devastating consequences, there is little to offer patients in the way of effective treatment to prevent or mitigate mucositis, and oral and gastrointestinal mucositis continues to present a significant challenge to patients undergoing cancer therapy. The few interventions that are supported by high-level evidence are not necessarily applicable for all types of OM, and their effects on tissues are not completely clear, leading to arbitrary protocols with great variance between medical centers.

Much has been learned about the complexities of OM pathogenesis and, consequently, potential targets for intervention have been identified. In addition, strategies have been implemented that reduce the damaging impact of treatment on normal tissue. This is perhaps most obvious in the adaption of intensity-modulated radiation therapy for patients with H&N cancers and of chemotherapy dose de-intensification for select patients.

The emergence of targeted and immune therapies has resulted in new oral mucosal toxicities (OMTs) that are distinct from the conventional mucositis induced by cytotoxic regimens in terms of pathobiology, clinical presentation, and management. Categories of targeted therapies commonly reported to be associated with OMTs include mammalian (mechanistic) target of rapamycin (mTOR) inhibitors

(mTORis), antiepidermal growth factor receptor (anti-EGFR) monoclonal antibodies and inhibitors, vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR) inhibitors, and B-rapidly accelerated fibrosarcoma (BRAF) inhibitors. Immune checkpoint inhibitors (ICIs) have also been associated with oral mucosal immune-related adverse events (OM-irAEs).

This objective of this review was to present current knowledge of the clinical presentation, epidemiology, pathogenesis, assessment, risk prediction, and current and developing intervention strategies for OM, OMTs and OM-irAEs.

Oral Mucositis Associated With Cytotoxic

Regimens

Epidemiology

It is estimated that there will be approximately 1.9 million new cases of cancer diagnosed in the United States this year.² Many patients will develop OM, with the highest proportion in patients treated with radiation therapy (RT) to the H&N or myeloablative chemotherapy treatment.

OM incidence and severity are largely underreported and are typically based on the adverse event (AE) reporting data associated with cancer treatment interventional studies. A clearer picture of incidence and trajectory is evident in studies in which the toxicity (ie, mucositis) is specifically evaluated. Moreover, variations in the prevalence and severity of OM might be related to the expertise and vigilance of the evaluators.³ Accordingly, the data presented below indicate the estimated frequency of OM in various patient populations.

Hematopoietic cell transplantation

From a patient's perspective, OM is the most severe toxicity reported by patients during HCT (42%).⁴ The prevalence and severity of OM depend on the type of transplant and conditioning regimen.

As demonstrated by OM rates among placebo-treated patients in clinical trials, aggressive conditioning regimens that include total body irradiation are associated with SOM frequencies as high as 98%.⁵ In a multicenter trial of patients with hemato-oncological diseases who were undergoing HCT (19 centers, 1841 patients), 71% of patients were diagnosed with OM, and 21.6% developed SOM.⁶ SOM was more prevalent in children (25.6%) and adults (24.4%) than in the elderly (9.2%). The risk of SOM was greater among adults, but not among children or the elderly, after conditioning for allogeneic HCT recipients compared with autologous transplant recipients (39.7% and 16.4%, respectively; $P < .001$).

OM frequency among patients undergoing HCT with reduced-intensity conditioning regimens versus myeloablative regimens revealed that any OM was found in 73.2% of patients who received reduced-intensity regimens (395 patients, 8 eligible studies) compared with 86.5% of patients

who received myeloablative regimens (245 patients, 6 studies; $P < .0001$).⁷ Mild OM was found in 22% to 45.5% and SOM was found in 5% to 53.8% of patients treated with reduced-intensity regimens. In contrast, mild OM was found in 15.9% to 56.7% and SOM was found in 19.4% to 83% of patients treated with myeloablative regimens.⁷ OM was more prevalent in patients who received methotrexate-based graft-versus-host disease (GvHD) prophylaxis in than those not treated with methotrexate (83.4% vs 55.4%; $P < .0001$).⁷ In patients who received tacrolimus/sirolimus-based GvHD prophylaxis, the incidence of OM was comparable to that in those who received cyclosporine/methotrexate-based GvHD prophylaxis.⁸

Head and neck radiation therapy

From 59.4% to 100% of patients with H&N cancer who were treated with RT or chemoradiotherapy (CRT) have OM, with SOM affecting approximately 65% of patients.^{9,10} The incidence is influenced by tumor site, radiation field, radiation technique, and the use of concomitant chemotherapy. In a meta-analysis of 12 prospective trials (1373 patients with H&N cancer) comparing the efficacy and toxicity of high-dose versus low-dose cisplatin-based CRT, the incidence of SOM was 75% and 40%, respectively ($P = .0202$).¹¹

Chemotherapy

OM incidence and severity vary widely, depending on the treatment regimen. In a meta-analysis assessing the incidence of chemotherapy-associated OM using all-phase clinical trial data, the average incidence of OM among patients with breast cancer who were treated with docetaxel, doxorubicin, and cyclophosphamide (>1400 patients) was 65%.¹² Approximately 5% of patients experienced SOM. The average incidence of OM in patients with lung cancer who were treated with platinum/gemcitabine (>1500 patients) was approximately 15% (1% SOM).¹² The average incidence of OM among patients with colon cancer who were treated with 5-fluorouracil-based chemotherapy (898 patients) was 14% for all grades (1.7% SOM).¹² However, among patients with colon cancer who were treated with the FOLFIRI protocol (Leucovorin Calcium [Folinic Acid], Fluorouracil, Irinotecan Hydrochloride), the incidence was higher (35% for all OM grades and up to 5% for SOM). Among patients with non-Hodgkin lymphoma (1444 patients), the estimated risk of OM was 6.6%.¹²

In pediatric patients, the incidence of OM was reported in 63.57% of chemotherapy cycles among those who were treated for solid and hematologic cancers. The incidence was higher in protocols using high-dose methotrexate.¹³ The rate of SOM was 8.44% and was strongly associated with the protocols that used high-dose methotrexate (10.5%) or a combination of methotrexate and cyclophosphamide (>28.3%).

Clinical Presentation and Outcomes

Acute oral mucositis

OM initially presents as erythema of the oral mucosa, progressing to atrophy and ulceration, often with pseudomembranous formations. The ulcers are characterized by irregular shape, and peripheral erythema (Fig. 1). The nonkeratinized mucosae of the buccal and labial mucosa, lateral and ventral tongue, soft palate, and floor of the mouth are most frequently affected (Fig. 2). In RT-induced OM, the areas affected correlate with the field of radiation (Fig. 3).

The clinical course of OM generally is predictable and is affected by the kinetics of anticancer treatment.¹⁴ Early clinical signs of chemotherapy-induced OM appear within approximately 3 to 4 days after infusion, with ulceration developing shortly thereafter. The intensity of OM peaks within approximately 2 weeks and generally heals spontaneously by 21 days after infusion.^{15,16} The pace of OM development, the worst severity, and the time for healing depend on the toxicity of the chemotherapy protocol. Accordingly, myeloablative HCT is expected to have faster and worse OM progress compared with nonablative chemotherapy protocols.

The clinical course of RT-induced OM is more prolonged, correlating with the fractionated treatment schedule. Clinical manifestations typically begin at cumulative radiation doses of approximately 15 to 20 grays (Gy) with standard fractionation, reaching full severity at 30 Gy, and lasting throughout the duration of RT. As radiation accumulates, ulcers become more confluent and disruptive, with spontaneous healing typically occurring 2 to 4 weeks after the completion of therapy.^{15–17}

The most common symptom of OM is significant pain of increasing intensity. In patients with H&N cancer, RT-induced OM was associated with clinically significant weight loss that required feeding tube insertion.^{9,18} In HCT recipients, OM was associated with the number of days with fever, days of injectable narcotic therapy, days of total parenteral nutrition, risk of significant infection, and mortality at 100 days post-HCT.^{1,19} Many patients reported OM as the most debilitating AE of cancer therapy.²⁰ Critically, OM negatively impacts local tumor control and patient survival because its presence often necessitates cancer treatment modifications, such as unplanned breaks or delays in treatment.²¹

Chronic oral mucositis

Chronic OM after H&N RT has been described, with atrophic, erythematous, and/or ulcerated lesions lasting >3 months after the completion of treatment (Fig. 4).^{22,23} Other long-term oral mucosal changes in postradiation patients include erythema, atrophy, and telangiectasias.²² Patients may also exhibit sensitivity or neuropathic pain, manifesting as a burning or scalding sensation in the oral



FIGURE 1. Oral Mucositis. Extensive oral mucositis partly covered by a yellow fibrin pseudomembrane, affecting the lips and oral mucosae after radiotherapy for oral carcinoma.

mucosa. Occasionally, this may result in intolerance to acidic, spicy, or hot foods. Approximately 8% of patients treated with RT to the H&N will develop chronic OM and, in 3.8%, it will present as ulceration.²³ It seems likely that the pathogenesis of chronic OM is different from what is described for the acute condition; and it is speculated that an immune-mediated response, shut-down of natural regenerative mechanisms, and involvement of the microbiome are elements in chronic OM.

Differential diagnosis

The diagnosis of OM can be made based on history, context of onset, and clinical findings, although other oral lesions can confound the diagnosis. The clinical course of OM may be complicated by secondary fungal (candidiasis) or viral (Herpes simplex virus [HSV]) infections, and these must be considered when lesions are unusual in appearance or last longer than expected. Ulcers induced by HSV reactivation differ clinically from OM in that they are typically localized on the keratinized mucosa of the tongue dorsum, the gingivae, and the hard palate. Bacterial, non-HSV viral infections and deep fungal oral infections should be considered in myelosuppressed patients. They can be differentiated from OM based on the clinical presentation, swab test, or, in the case of deep fungal infection, by a biopsy. Because patients with cancer are often treated with polypharmacy, the differential diagnosis of oral ulceration may include drug eruption and erythema multiforme/Stevens–Johnson syndrome.

Risk Factors

Risk factors can be classified as patient-related, tumor-related, and treatment-related factors.

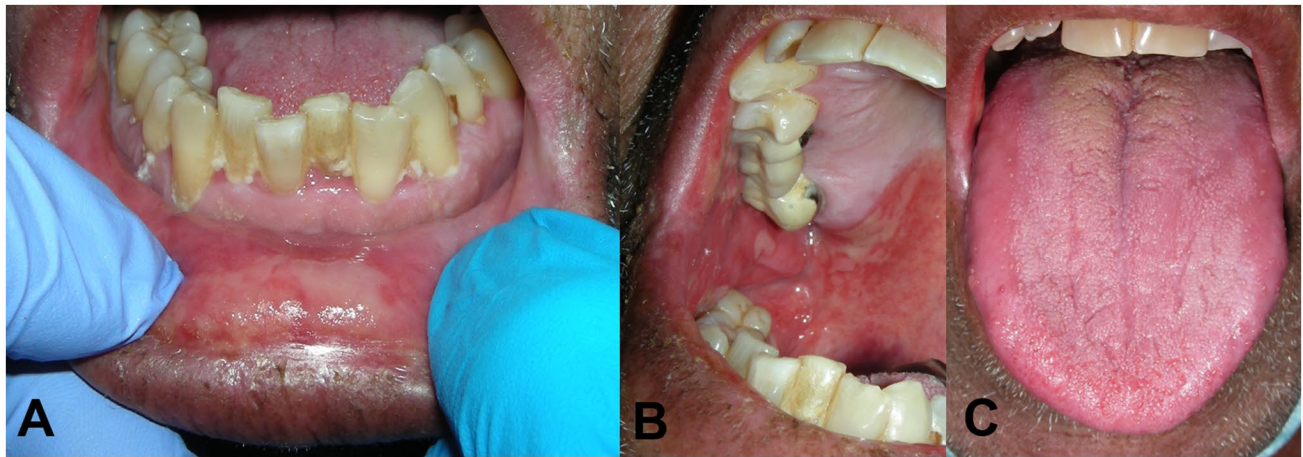


FIGURE 2. Chemotherapy-Induced Oral Mucositis. The ulcers are partly covered by a yellow fibrin pseudomembrane in a patient with colon cancer, affecting only nonkeratinized mucosae, ie, (A) labial mucosa, (B) buccal mucosa, and soft palate, but not affecting (A) the keratinized gingiva, (B) hard palate, or (C) dorsal tongue.

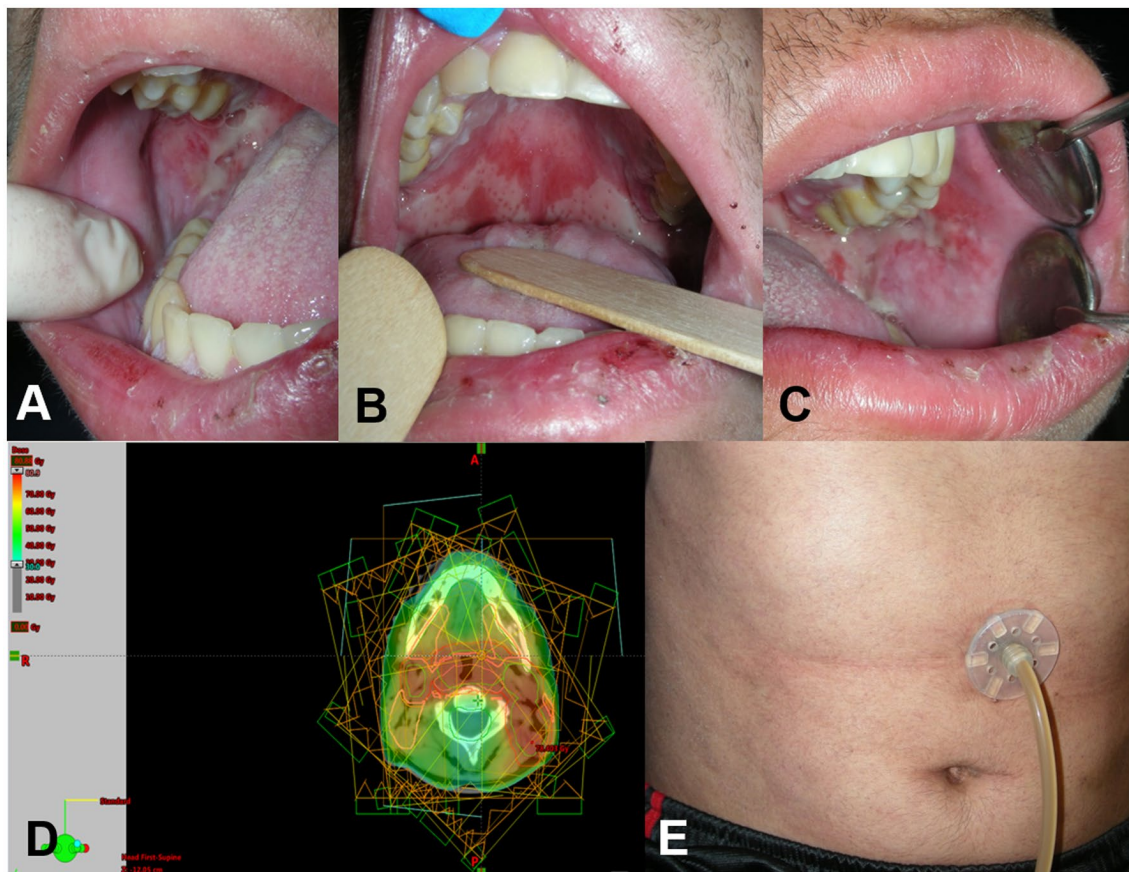


FIGURE 3. Radiotherapy Induced Oral Mucositis. Oral mucositis affecting bilaterally (A,C) the posterior buccal mucosae and (B) the soft palate after radiotherapy for nasopharyngeal carcinoma. (D) Note that the extension of the oral ulceration is in accordance with the radiation exposure. (E) Percutaneous endoscopic gastrostomy was needed for feeding.

Patient-related factors

Sex has been reported to have an influence on mucositis risk because, in most studies, female sex is linked to increased risk.²⁴ However, this may be driven by dosimetric parameters (ie, calculating the risk per kilogram of body weight or per square meters of body surface area).^{24,25}

An individual's low baseline performance status may be related to increased mucositis risk.²⁵ There is inconsistent evidence regarding the influence of age, smoking, oral hygiene, and body mass index on mucositis risk.^{24,26} The risk of mucositis may be influenced by genetic variants in drug-metabolizing pathways, immune signaling, and



FIGURE 4. Chronic Persistent Oral Mucositis. Ulceration and atrophy on the tongue of a patient aged 88 years >5 months after the last dose of radiotherapy for oral squamous cell carcinoma.

cell injury-repair mechanisms, although the evidence is limited or conflicting (see Supporting Table 1). Systemic factors, such as comorbidities, medication use, and previous therapy, have been associated with increased risk (see Supporting Table 2). Numerous variables had conflicting evidence, such as neutropenia/leukopenia. Uncontrolled diabetes mellitus was suggested as a potential risk factor of persistent chronic OM related to RT.²²

Tumor-related factors

Clinical features of the tumor, such as site and stage, may influence the risk of mucositis and severity.²⁴ In patients with H&N cancer who are receiving RT, these characteristics determine the radiation plan (field and dose) and thus influence the exposure of the mucosal tissues and the development and severity of mucositis.

Treatment-related factors

An increased risk of mucositis has been reported with increasing doses of radiation,²⁷ myeloablative conditioning before HCT,²⁸ and chemotherapy, such as methotrexate and melphalan.²⁵ Altered, fractionated RT (eg, accelerated fractionation of 6 fractions per week or 2 daily fractions of 2 Gy each) may be associated with increases in mucositis frequency and duration.^{29,30} Conversely, intensity-modulated radiation therapy, which enables the design of radiation scattering, can allow a reduction in toxicity, for example, by planning a cumulative exposure <30 Gy, when possible.²⁷

Risk factors in pediatric patients

Among children, low body weight, anxiety level, nausea/vomiting, and previous OM are associated with an increased risk of developing OM.³¹ An association was reported between OM and leukopenia and neutropenia, as well as between OM and lymphopenia in patients with solid

tumors.^{31,32} There is conflicting evidence regarding the association between platelet level and OM.^{31,32} Like in adult patients, genetic variants may determine mucositis risk (see Supporting Table 1).^{31,33} Reported microbial risk factors include HSV type 1, oral *Candida* species, and unspecified bacterial infections.^{32,34}

Hematologic malignancies like lymphoma and germinal tumors like neuroblastoma, nephroblastoma, and retinoblastoma reportedly increased the risk of mucositis induced by chemotherapy.^{34,35} Protocols using high-dose methotrexate, daunorubicin, doxorubicin, vincristine, etoposide, busulfan, and cytarabine were presented as potential risk factors for OM in pediatric cancer patients.^{13,31}

Pathobiology

Historically, mucositis pathogenesis was described using a simplistic approach, which ascribed normal tissue injury of mucosa as the sole consequence of the indiscriminate effects of radiation or chemotherapy on the rapidly dividing normal cells of replenishing tissues like the gastrointestinal mucosa. This idea was overturned by the results of many studies indicating that direct cell injury (direct DNA double strand breaks [DSBs]) could only account for approximately one-third of the observed injury. Consequently, the complexity of the pathogenesis of chemotherapy-associated or RT-associated normal tissue injury was realized and summarized in a model that broadly compartmentalizes the biological sequence into 5 broad stages. Although such a model is convenient, it minimizes the intricacies of each stage and does not adequately relate the biological or clinical dynamics of mucositis development, especially for cases in which the tissue is repeatedly challenged, as with fractionated radiation. Nonetheless, the model does provide a snapshot summary of the molecular and cellular events and pathways that terminate in mucositis development. The 5 stages are (Fig. 5): *initiation, up-regulation and activation* (primary damage response), *signal amplification, ulceration*, and *healing*.³⁶ This offers a convenient summary of the complex, nonlinear progression of injury as the various stages and associated biological processes interrelate and overlap.

The molecular events that characterize the initiation phase happen almost immediately after patients receive chemotherapy or RT. Although there is biological havoc within the tissue, clinically, the mucosa seems unaffected. This finding speaks to the need to initiate steps to attenuate the risk of mucositis before and at the time of treatment.

The initiation stage occurs throughout the cellular and tissue compartments of the mucosa and submucosa. This stage is characterized by direct damage to DNA, oxidative stress responses mediated by reactive oxygen species (ROS), and activation of the innate immune response.^{37,38} Both direct and

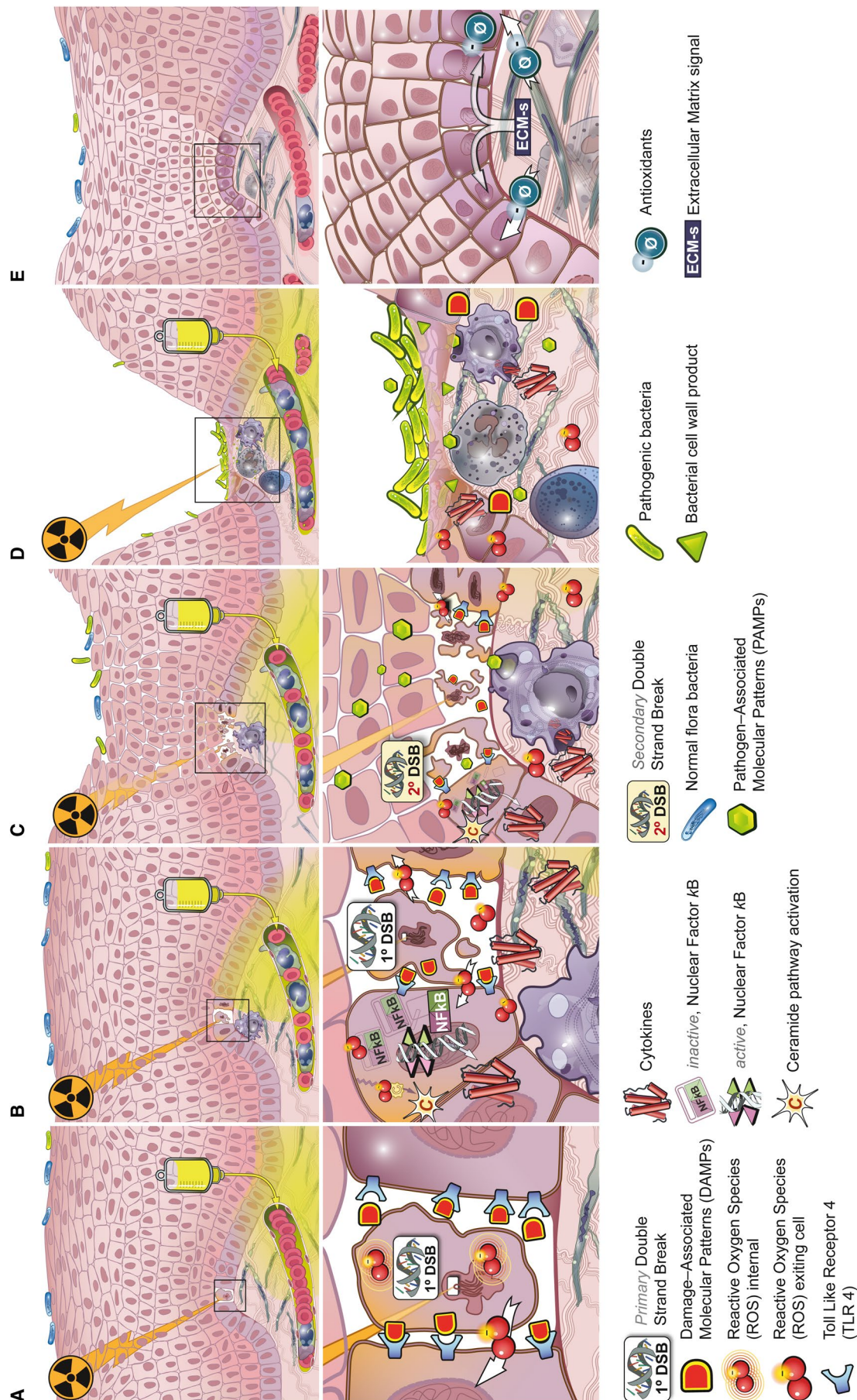


FIGURE 5. Five Stages Delineate the Biological Sequence of Mucositis Pathogenesis. Although convenient as a tool to describe the key biological elements involved, the process is more complex and interactive than is suggested by a simple set of illustrations. Nonetheless, both radiation-induced and chemotherapy-induced oral mucositis share similar components, including targeting the basal epithelial layer. Once apoptosis or necrosis affects the basal cells, epithelial renewal ceases, and ulceration ensues. (A) In the *initiation phase*, direct cell injury in the form of radiation-induced or chemotherapy-induced double strand breaks accounts for approximately 30% of basal cell injury. Most injury, however, is initiated by the production of ROS and activation of the innate immune response. These 3 events, which occur simultaneously, are interactive in initiating the biological cascade that results in apoptosis and necrosis of basal stem cells. Cells destroyed by the direct effects of cytotoxic agents produce DAMPs. ROS resulting from the effects of agents on cellular water are highly biologically active. (B) In the *up-regulation and activation phase*, both ROS and DAMPs activate key transcription factors, such as NF-κB, and DAMPs activate pattern-recognition receptors, such as TLR-4. Consequently, genes are activated and expressed, resulting in the production of proinflammatory cytokines and signaling molecules. At the same time, the ceramide pathway is activated after lipoperoxidation of the cell membrane. Damaging enzymes (matrix metalloproteinases) affect the connective tissue. Naturally occurring defense mechanisms, such as the control of oxidative stress by antioxidant enzymes, are overwhelmed. (C) In the *signal-amplification phase*, as the process snowballs, the number of signaling molecules (including cytokines) increases, providing positive feedback to amplify the effects. Increased epithelial permeability resulting from tight junction breaks provides a conduit for surface bacteria cell wall products (PAMPs) to fuel the biological fire. (D) In the *ulceration phase*, with no replenishment, the epithelium becomes atrophic and ultimately ulcerates. Colonizing bacteria continue to spew out PAMPs, damaging enzymes continue to affect the connective tissue, and compositional changes in the cellular infiltrate are noted. (E) In the *healing phase*, once the cytotoxic challenge is completed (no additional radiation or chemotherapy), spontaneous healing occurs, with messaging from the submucosa stimulating epithelial proliferation and guiding differentiation.

indirect damage to cellular DNA precipitates DSBs, leading to apoptotic and necrotic tissue changes. These degeneration products (damage-associated molecular pattern molecules [DAMPs]), such as alarmins, bind to pattern-recognition receptors, such as Toll-like receptors (TLRs) (ie, TLR-4), to escalate injury by activating the innate immune response. Simultaneously, water in cells undergoes hydrolysis to generate damaging superoxides and hydrogen peroxide. In the early stages of cellular stress, internal defense mechanisms, such as the deoxidizing enzymes superoxide dismutases, are ramped up. This happens either through activation of transcription factors, such as nuclear factor κ -B (NF- κ B) and nuclear factor erythroid 2-related factor 2 (Nrf2), or through intracellular superoxide. However, these are quickly overwhelmed by the aggressiveness of the regimen-related challenge.

During the second stage, ROS and the innate immune response further activate several transcriptional factors, including NF- κ B, Wnt, p53, and their associated canonical pathways. The NF- κ B pathway is one of the most studied. Once activated, NF- κ B-mediated gene expression results in increased production of proinflammatory cytokines (such as tumor necrosis factor α [TNF- α] and interleukin [IL]-1 β , IL-4, IL-6, and IL-18) and cytokine modulators, stress responders (such as cyclooxygenase 2 [COX-2]), and cell adhesion molecules, which, in turn, can lead to cell apoptosis. The TLR signaling pathway and various kinase pathways (such as mitogen-activated protein kinase [MAPK]) are playing a role in this process. Cross-talk between all of the active elements is robust.

Other identified pathways that may lead to apoptosis include the ceramide pathway, which affects the cell membrane. DNA DSBs can directly activate ceramide synthase, with the consequent generation of ceramide. In addition, ROS lead to lipid peroxidation, sphingomyelinase activation, and the hydrolysis of membrane sphingomyelin to yield ceramide. Although ceramide is considered a proapoptotic molecule, its accumulation is a signal for increased membrane permeability and ultimately break of the epithelial cells.

During the signal-amplification phase, the molecules induced by this primary response further alter local tissue response by amplifying NF- κ B and other pathways through feedback mechanisms. For example, released TNF- α sustains NF- κ B activity and, at the same time, initiates the activation of MAPK signaling. The early breakdown of cells spills additional DAMPs into the tissue, which, in turn, increases NF- κ B. The DAMPs also drive the innate immune response. Furthermore, while the intercellular bridges break, the epithelial cells start to spread apart, and the bacteria penetrate from the oral cavity into the tissue. The immune system fights these bacteria and, in turn, generates pathogen-associated molecular pattern (PAMPs) molecules, which induce additional NF- κ B activity. The end result is a vicious cycle that amplifies the damage. Furthermore, while the RT or chemotherapy continues, the influx of ROS endures and

constantly feeds the development of proinflammatory cytokines. Simultaneously, cytotoxic therapy-induced mucosal damage occurs through connective tissue fibrinolysis and the stimulation of tissue-damaging matrix metalloproteinases, which damage the extracellular matrix. On the epithelial surface, the oral flora undergoes a shift toward more pathogenic bacteria.

Cumulatively, these early biological events lead to progressive tissue injury and loss of epithelium continuity, which manifest clinically as ulceration and atrophic changes. The ulcerative stage is the most clinically significant because patients develop symptomatic, deep ulcers that are susceptible to infection. Oral bacteria colonizing the ulcers play a role in extending mucosal damage and increasing its severity by direct stimulation of infiltrating macrophages, neutrophils, and lymphocytes to secrete additional proinflammatory cytokines.³⁹ This harmful process continuously increases, leading to a storm of ROS, PAMPs, DAMPs, and proinflammatory cytokines.

Finally, at the end of the RT or chemotherapy, spontaneous healing of the ulcers occurs. Once the trigger for this process is held, the redox equilibrium starts the shift back, and the process gradually becomes self-contained. Stimulated by signaling molecules from the extracellular matrix, epithelial migration, proliferation, and differentiation occur, and local microbial flora is reestablished. This final stage leads to renewal of the mucosa, restoring its continuity; however, the genetics of the new epithelium differ from the original epithelium. This may result in a lower threshold for subsequent cycles of RT or chemotherapy.

Outcome Assessment Measures

Clinician-reported outcome measures

Several instruments are available to record the severity of OM and provide guidance for supportive care interventions or cancer treatment modifications.⁴⁰ The frequently used scales are detailed in Table 1. The World Health Organization (WHO) scale is routinely used in clinical practice and clinical trials. This simple, 5-point scale combines both subjective and objective measures of OM.⁴¹ The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0, is often used in clinical trials to document AEs of antineoplastic therapies.⁴² Focusing on functionality to assess OM severity, this 5-point scale documents pain severity and the patient's ability to eat. The Radiation Therapy Oncology Group's 4-point scale is used to record the severity of RT-induced OM.⁴³

Clinical research scales are quantitative in nature and assess objective variables. The Oral Mucositis Assessment Scale, for example, permits a subanalysis of mucosal damage across anatomic sites, measuring erythema and ulceration. This scale has been validated in both adult and pediatric populations and was correlated closely with patient symptoms.^{44,45}

TABLE 1. Clinical Oral Mucositis Assessment Scales

SCALE	GRADE 0	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE-THREATENING)	GRADE 5 (DEATH)
WHO	No findings	Oral erythema and soreness; no ulcers	Oral erythema, ulcers; solid diet tolerated	Oral ulcers; liquid diet only	Oral alimentation impossible	NA
NCI-CTCAE	None	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain, interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
RTOG	No change over baseline	Irritation; may experience mild pain, not requiring analgesic	Patchy mucositis that may produce an inflammatory, serosanguinous discharge; may experience moderate pain requiring analgesia	Confluent, fibrinous mucositis; may include severe pain requiring narcotic	Ulceration, hemorrhage, or necrosis	NA

Abbreviations: NA, not applicable; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.

Patient-reported outcome measures

Patient-reported outcome data are important contributors to the overall assessment of OM severity. The 0 to 10 Numeric Rating Scale is a unidimensional measure widely used because of its ease of administration.^{46,47} Patients rate the severity of oral pain on an 11-point horizontal bar, with 0 indicating no pain at all and 10 indicating the worst pain possible. The Oral Mucositis Daily Questionnaire, as well as its weekly version (the Oral Mucositis Weekly Questionnaire), measure the symptoms of OM, including mouth and throat soreness, and their impact on patient well-being and function.^{48,49}

The Functional Assessment of Cancer Therapy–Head and Neck (FACT–HN) scale includes the FACT–General, a multidimensional quality-of-life (QoL) instrument specifically designed for use in patients with cancer, and an H&N cancer-specific subscale.⁵⁰ The FACT–HN is used to evaluate the impact of OM on the QoL of patients with H&N cancer across the physical, functional, emotional, and social domains. Similar to the FACT system, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) is designed to assess the QoL of patients with cancer and is supplemented by disease-specific modules. In its most recent version, the EORTC QLQ–HN43 module captures side effects and QoL effects of all H&N cancer treatment modalities across 19 different scales.⁵¹ As one of the standard instruments for measuring QoL in patients with H&N cancer, the EORTC QLQ–HN43 has been internationally validated and is available in 17 language versions.

Measurement of oral mucositis in children

Documenting OM severity in children can be challenging. Depending on age, patients' ability to comprehend instructions, tolerate oral cavity examination, and express the symptoms may require reliance on parent-proxy reports.⁵² Few of the most common adult-validated OM scales (ie, the Oral Mucositis Assessment Scale and the Oral Mucositis

Daily Questionnaire) have been evaluated in children.^{44,53} The Children's International Mucositis Evaluation Scale, a pediatric-specific measure of OM, has been validated for use in children and adolescents aged 8 years or older who are undergoing HCT (Fig. 6).⁵⁴

Management of Oral Mucositis

In general, oral care for patients with cancer includes several principles: prevent infection, control pain, maintain oral function, improve QoL, and manage concomitant oral complications.⁵⁵ These principles are not limited to OM but, rather, address all types of oral complications. The section below details the aspects related specifically to OM.

Measures that are specific for OM management include either prevention or symptom management. Currently, there is no intervention for therapeutic intention. The main factor in OM prevention is tissue sparing by RT treatment planning and the use of RT techniques that are able to spare the noninvolved oral mucosal surface. Additional measures are addressed in the evidence-based guidelines developed by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (Table 2^{53,56–63}).⁶⁴ The guideline categories include a *recommendation*, a *suggestion*, or *no guideline possible*. A recommendation was reserved for interventions with the strongest evidence, supported by multiple randomized controlled trials, at least one of them with no major flaws. A suggestion was assigned to interventions that had consistent results in multiple randomized controlled trials. Accordingly, many of the reported interventions in the literature did not reach a recommendation or suggestion guideline level. Assessments of the evidence for these interventions are available in the full set of guidelines articles.^{56–66}

Table 2 lists the recommended or suggested interventions that are specific to particular populations of patients with cancer. Cryotherapy is recommended concomitantly

CHILDREN'S INTERNATIONAL MUCOSITIS EVALUATION SCALE (ChIMES)

PAIN

1. Which of these faces best describes how much pain your child feels in their mouth or throat today? Circle one.

					
0	1	2	3	4	5
No hurt	Hurts a little bit	Hurts a little more	Hurts even more	Hurts a whole lot	Hurts worst

FUNCTION

2. Which of these faces shows how hard it is for your child to SWALLOW their saliva/spit today because of mouth or throat pain? Circle one.

						☐ Can't tell
0	1	2	3	4	5	
Not hard	Little bit hard	Little more hard	Even harder	Very hard	Can't swallow	

3. Which of these faces shows how hard it is for your child to EAT today because of mouth or throat pain? Circle one.

						☐ Can't tell
0	1	2	3	4	5	
Not hard	Little bit hard	Little more hard	Even harder	Very hard	Can't eat	

4. Which of these faces shows how hard it is for your child to DRINK today because of mouth or throat pain? Circle one.

						☐ Can't tell
0	1	2	3	4	5	
Not hard	Little bit hard	Little more hard	Even harder	Very hard	Can't drink	

PAIN MEDICATION

5. Has your child taken medicine for any kind of pain today?

☐ Yes ☐ No

If yes, did your child need the medicine because they had mouth or throat pain?

☐ Yes ☐ No

APPEARANCE

6. Please look in your child's mouth. Can you see any mouth sores (ulcers)?

☐ Yes ☐ No ☐ Can't tell

FIGURE 6. The Children's International Mucositis Evaluation Scale (ChIMES). Source: Jacobs S, Baggott C, Agarwal R, et al. Validation of the Children's International Mucositis Evaluation Scale (ChIMES) in paediatric cancer and SCT. *Br J Cancer*. 2013;109:2515-2522.⁵⁴

with the bolus injection of high-dose melphalan in patients undergoing autologous HCT.⁵⁷ Several cryotherapy protocols are described in the literature, with different amounts of

time that the ice water needs to be held in the mouth, and all were reported to be effective⁵⁷; however, longer durations may be more difficult for patients. Photobiomodulation (PBM)

TABLE 2. Management of Oral Mucositis Based on the 2020 Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology Guidelines^a

INTERVENTION	AIM	MASCC/ISOO GUIDELINE CATEGORY	RATIONALE	SPECIFICATIONS
1. Basic oral care (Hong 2019 ⁵⁶)	Prevention	Suggestion (expert opinion)	Increases patients' awareness and enhances their compliance with routine oral care	Includes dental evaluation and treatment, as indicated, before cancer therapy; patient education on the benefits of basic oral care to improve self-management during cancer treatment; and the use of saline and sodium bicarbonate rinses to increase oral clearance; Additionally, implementing multi-agent combination oral care protocols
2. Cryotherapy (Correa 2020 ⁵⁷)	Prevention	Recommendation	Cold-induced local vasoconstriction limits delivery of the chemotherapeutic agent to the oral mucosa	In patients receiving bolus doses of 5-fluorouracil and in patients undergoing autologous HCT conditioned with high-dose melphalan
3. Photobiomodulation therapy (Zadik 2019 ⁵⁸)	Prevention	Recommendation	Stimulates and promotes wound healing	Specific protocols for HCT patients as well as patients who have cancer treated with H&N radiotherapy with or without concurrent chemotherapy; the use of PBM in known tumor areas should be considered cautiously
4. Benzylamine (Ariyawardana 2019 ⁵⁹)	Prevention	Recommendation/Suggestion	Anti-inflammatory	In patients receiving moderate-dose H&N radiation (up to 50 Gy) and patients who have H&N cancer treated with chemoradiation
5. KGF-1 (Logan 2020 ⁶⁰)	Prevention	Recommendation	Stimulates the proliferation and differentiation of epithelial cells; KGF-1 has antiapoptotic, antioxidant, and anti-proinflammatory effects, inducing tissue protection	In patients receiving high-dose chemotherapy and TBI-based conditioning regimens before autologous HCT
6. Glutamine (Yarom 2019 ⁶¹)	Prevention	Suggestion	Maintains cell homeostasis and promote cell survival against metabolic stress	In patients undergoing H&N chemoradiation; caution due to the higher mortality rates seen in HCT patients treated with parenteral glutamine
7. Honey (Yarom 2020 ⁶²)	Prevention	Suggestion	Wound-healing and antimicrobial properties	In patients with H&N cancer receiving radiotherapy with or without chemotherapy; topical and systemic administration; strict oral hygiene is advised
8. Patient-controlled analgesia (Saunders 2020 ⁶³)	Treatment	Recommendation	Pain management	In patients undergoing HCT
9. Topical morphine 0.2% (Saunders 2020 ⁶³)	Treatment	Suggestion	Pain management	In patients with H&N cancer treated with chemoradiation

Abbreviations: Gy, grays; H&N, head and neck; HCT, hematopoietic cell transplantation; KGF-1, keratinocyte growth factor-1; MASCC/ISOO, Multinational Association for Supportive Care in Cancer/ International Society of Oral Oncology; PBM, photobiomodulation; TBI, total body irradiation.

^aSee Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126:4423-4431.⁶⁴

therapy is beneficial for preventing OM using the application of certain PBM protocols.⁵⁸ On the basis of the current literature, benzydamine 0.15% mouthwash effectively prevents OM in patients who receive up to 50 Gy RT or CRT. For example, it may be beneficial for patients undergoing palliative RT or RT to the H&N for lymphoma.⁵⁹ Keratinocyte growth factor-1 is delivered by intravenous injections at a dose of 60 mcg/kg once daily for 3 days before and after myelotoxic HCT.⁶⁰ There is evidence that 10 grams of oral glutamine taken from once to 3 times daily throughout a 6-week, concomitant CRT course reduces OM severity and its associated pain in patients with H&N cancer.⁶¹ Combined topical and systemic administration of a variety of honey products has consistently demonstrated efficacy.⁶² Patient-controlled analgesia includes an intravenous morphine infusion with a patient-controlled pump.⁶³ A topical 0.2% morphine rinse has been suggested for managing pain related to RT-associated OM.⁶³

Although the guidelines are evidence-based, they may not be applicable globally. For example, benzydamine is available *over the counter* in some European countries but is unavailable in the United States. In addition, PBM therapy includes many types of laser devices and protocols, and each type is registered only in certain countries, limiting access to this treatment modality. Extensive collaboration is needed to translate the protocols used successfully on one device to other devices.⁵⁸ Therefore, the guidelines should be adjusted according to the practical considerations of the clinic and patient's preference.

Optimal nutritional support must be maintained throughout the duration of cancer therapy to mitigate the risk of OM-associated nutritional deterioration and subsequent interruption of anticancer therapy. Potential sources of irritation, such as spicy, acidic, or rough (crunchy) foods, may exacerbate the discomfort of OM and should be avoided. The use of liquid dietary supplements should be considered when dietary measures are insufficient. In severe cases, gastrostomy feeding or total parenteral nutrition may be warranted (Fig. 3E).

Although several interventions for the prevention or treatment of OM have been trialed in pediatric populations, no specific guidelines currently exist for children undergoing cancer therapy because of insufficient and/or conflicting evidence.⁶⁷ Although the suggestion to implement basic oral care protocols encompasses all cancer treatment modalities and age groups, including pediatric patients, other interventional protocols in this patient population are extrapolated from the currently available evidence for adult patients with cancer. Adaptations are advised to increase patients' acceptance and tolerability toward the intervention. For example, the application of oral cryotherapy using flavored popsicles instead of ice or ice water in younger patients may increase compliance.⁶⁸

Targeted Anticancer Therapy-Associated Oral Mucosal Toxicity

Epidemiology

mTORis, such as everolimus, sirolimus, temsirolimus, and ridaforolimus, are strongly associated with the development of aphthous-like ulcers. In a meta-analysis of 1455 patients with solid tumors who received everolimus, 973 (67%) had stomatitis, and 9% had grade 3 or 4 stomatitis.⁶⁹ In a review of 44 studies that included 2822 patients who had lung cancer and were treated with mTORis, OMT was identified as the most frequent AE (73.4%).⁷⁰ Severe OMT was reported in 30.9% of all patients with OM (grade 3, 20.7%; grade 4, 10.2%), and it was responsible for dose reductions in 27.3% of patients and even for drug discontinuations in 13.1%.

Regimens that include chemotherapy and anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab, may result in an increased risk for the development of OMT. Severe OMT was reported in 8% of patients with colorectal cancer who received chemotherapy and anti-EGFR monoclonal antibodies regimens compared with 2% in patients who received chemotherapy alone, with a relative risk (RR) of 3.44 (95% CI, 2.66–4.44; $P < .00001$).⁷¹ Likewise, all-grade OMT was noted to occur in 2% to 50% of patients who received lapatinib, an HER2 inhibitor, with an RR of 1.67 (95% CI, 1.02–2.3; $P < .04$).⁷² The small-molecule EGFR inhibitors that have been reported in association with mucositis are erlotinib, afatinib, and gefitinib.⁷³

Oral mucosal lesions have also been reported in patients treated with VEGFR inhibitors (eg, sorafenib, sunitinib, pazopanib, and cabozantinib). Sorafenib-induced OMT has a reported incidence of 5% to 33% in patients with solid tumors, with an all-grade RR of 2.9 (95% CI, 2.26–3.73; $P < .00001$).⁷⁴ Likewise, sunitinib-induced OMT has a similar incidence of 5% to 32% in patients with solid tumors, with an RR for all-grade stomatitis of 1.88 (95% CI, 1.36–2.59; $P = .0001$).⁷⁵

Clinical Presentation

Unlike the predictable course of conventional mucositis, mucosal injury associated with targeted therapies is variable. Importantly, OMTs associated with targeted therapies are phenotypically distinct from the OM seen with cytotoxic drugs. mTORi-OMT (also known as mTORi-associated stomatitis) is characterized by aphthous-like lesions that present as discrete, well demarcated, ovoid, superficial ulcers and typically measure <0.5 cm in diameter.^{76,77} Lesions are surrounded by an erythematous halo and are localized to the nonkeratinized mucosa (Fig. 7). Ulcers >0.5 cm occur less frequently and result in severe pain. Unlike conventional mucositis, mTORi-OMT is often associated with nonspecific rash. With a more rapid course than conventional mucositis, ulcers develop acutely several days after the start of an mTORi (median time to onset, 10 days) and resolve within a week. In approximately

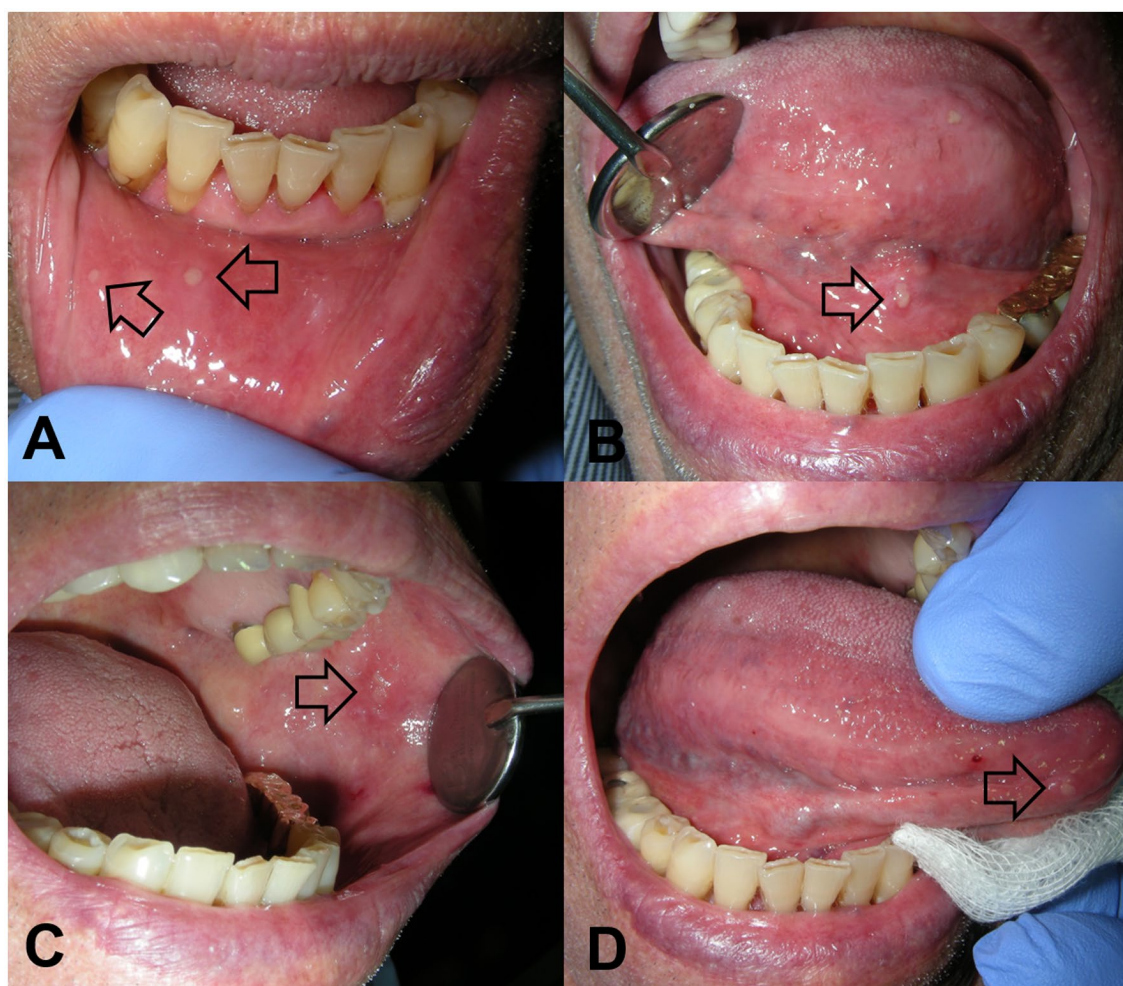


FIGURE 7. Aphthous-Like Ulcers (arrows) in a Patient Treated With Targeted Therapy. (A-D) Intraoral pictures of the patient at different points.

27% of patients who develop mTORi-OMT, an mTORi dose reduction is needed to continue with the treatment.⁷⁰

Monotherapy with EGFR inhibitors or anti-EGFRs causes relatively few and mild mucosal lesions. These range in presentation from moderate erythema to limited, superficial ulcers involving the nonkeratinized mucosa.⁷⁷ However, because EGFR inhibitors are typically used in combination with cytotoxic therapies, their addition leads to an increase in mucositis incidence and severity, presenting with both superficial and deeper ulcers. Interestingly, the toxicities of ibrutinib, a Bruton's tyrosine kinase inhibitor, overlap with the toxicity profile associated with EGFR inhibitors.⁷⁸

The main oral AEs reported in association with VEGF inhibition include nonspecific OMT, dysgeusia, and xerostomia, occurring either alone or concurrently.⁷⁹ In some cases, the reported OMT may present with erythema or discrete ulcers of the nonkeratinized mucosa. However, the typical manifestation is more of a diffuse oral mucosal sensitivity or dysesthesia, with otherwise normal-appearing mucosa. Symptoms develop in the first weeks of treatment.^{79,80} Overall, the occurrence of oral AEs appears to be associated

with an increased risk of developing hand-foot skin reaction.^{79,81} Indirectly, hyposalivation may render the oral mucosa sensitive to repeated friction from normal function.^{79,82} Therefore, the xerostomia reported in association with VEGF inhibition may contribute to the mucosal toxicity. In addition, sunitinib was reportedly associated with additional types of oral mucosal changes: cheilitis and lichenoid reaction.^{80,83}

Pathobiology

The pathobiology for oral mucosal lesions caused by targeted cancer therapies has only been preliminarily investigated. Targeted agents are mechanistically distinct and are designed to interfere with key pathways in tumor growth or development that apparently affect normal tissue. The main pathways of the agents that are associated with oral mucosal ulcerative lesions are EGFR, mTOR, VEGF, VEGFR, and BRAF. Although not well elucidated, the mucosal toxicities they ensue result from the very same mechanisms of action. The synergistic use of targeted agents with conventional cytotoxic therapy or with each other, however, renders the detection of the driver of mucosal damage difficult. Moreover, the concurrent administration of therapies may result in

more mucosal damage than that seen with either therapy individually, further complicating matters.

Outcome Assessment Measures

Currently, validated, targeted, therapy-specific grading scales are scarce. OMTs associated with targeted therapies are assessed using the scales developed for conventional OM, particularly the NCI-CTCAE and WHO scales (see Outcome Assessment Measures, above). Because these scales are not specifically designed to grade OMTs caused by targeted cancer therapies, morbidity may be underestimated. The use of patient-reported outcome measures is further indicated, particularly in the context of oral AEs with lack of clinical signs, such as the oral mucosal sensitivity (dysesthesia) observed with VEGF/VEGFR inhibition. A 4-point scale (grades 0–3) has been suggested to assess mTORi-OMT severity.⁸⁰

The Multinational Association of Supportive Care in Cancer EGFR Inhibitor Skin Toxicity Tool (MESTT) has been proposed for the assessment of mucocutaneous AEs caused by EGFR inhibitors.⁸⁴ Reported as *oral mucositis*, OMT is classified according to its clinical presentation, the patient's level of pain, and their ability to eat and drink. This 4-point scale ranges from grade 1 (mild erythema or edema, asymptomatic) to grade 4 (erythema and ulceration, cannot tolerate oral intake; requires tube feeding or hospitalization). With increased focus on health-related QoL, the MESTT also introduces *hyposalivation* and *taste* scales.

Management

The management of targeted therapy-induced OMT generally is focused on symptom management. Current interventions are based mainly on expert opinion and include basic oral care measures and strategies that follow therapy for other mucosal inflammatory conditions.⁸⁵

In the absence of confirmatory trial data, the European Society of Medical Oncology published expert opinion recommendations for targeted therapy-associated stomatitis with a focus on mTORi-OMT.⁸⁶ Aside from basic oral care and oral hygiene recommendations, the use of high-potency steroids (topical, intralesional, or systemic) was recommended as first-line therapy for established mTORi-OMT based on the clinical resemblance of mTORi-associated stomatitis to aphthous stomatitis.^{77,85} A list of topical steroidal treatments is proposed based on evidence in other oral mucosal diseases and the experience of the authors (Table 3).⁸⁷ Some of the formulations in this list are not available commercially and may need to be compounded. No comparative studies are available to support its benefit for targeted therapy-related OMT. There appears to be potential benefit from the use of a daily dexamethasone 0.5 mg/5 mL oral solution in mitigating the development of mTORi-OMT.^{88,89} Intralesional

injections of triamcinolone acetonide (up to 40 mg/mL infiltrated in a few points around the perimeter of the lesion) may be beneficial for resistant or highly symptomatic OMT and can be administered as a single dose or in cycles of injections 2 to 3 weeks apart.⁹⁰

Immune Checkpoint Inhibitor-Associated Oral Mucosal Toxicity

Epidemiology

OM-irAEs are relatively rare among patients treated with ICIs. In a meta-analysis of 18 RCTs ($n = 11,465$ patients), 2.7% of patients experienced stomatitis, and 0.2% had severe OM-irAEs.⁹¹ In a retrospective study of 4683 ICI-treated patients, 252 (5.4%) demonstrated mucosal lesions.⁹² Of 8637 patients from a national insurance claims database, OM-irAEs were reported in 1.5% of patients treated with ICIs.⁹³

Clinical Presentation

Reports on OM-irAEs are limited and are predominantly associated with antiprogrammed cell death protein-1/programmed cell death ligand 1 (anti-PD-1/PD-L1) agents (Fig. 8). The mean onset of oral irAEs is 3 months from the initiation of treatment, and most AEs occur within the first 12 months.^{92,94,95} However, late onset has been reported, with toxicity developing more than a year after therapy. Mucosal lesions include those typically associated with cell-mediated immune dysfunction, described as *lichenoid*, as well as vesiculobullous lesions, which are antibody-mediated. Oral lichenoid reactions represent the most frequent OM-irAEs observed, presenting with symmetric, white reticulations and, to a lesser extent, with erythema and/or ulcers. Histopathology is consistent with lichenoid mucositis.^{94,95} These oral lichenoid reactions are usually asymptomatic and occur in an isolated manner, although they can be accompanied by skin, nail, or genital involvement.⁹⁵ Other reported inflammatory/antibody-mediated mucosal manifestations include erythema multiforme-like inflammation, pemphigoid, and Steven-Johnson syndrome.^{92,94,96–100} Immune-mediated sialadenitis presenting with oral sicca is the second most common oral irAE reported in association with ICIs.^{101–103} Dry mouth can be very severe, causing mucosal friction.¹⁰²

Pathobiology

Although the pathogenesis of oral mucosal lesions secondary to ICIs has not been studied in depth, based on their lichenoid-like presentation, it seems probable that the infiltration of normal tissues with activated T cells catalyzes a local cell-mediated immune response.^{104,105}

Currently approved checkpoint inhibitors target the molecules cytotoxic T-lymphocyte-associated protein 4

TABLE 3. Topical Treatments Proposed for the Management of Targeted Therapy Related-Oral Mucosal Toxicities and Oral Ulcerative Mucosal Immune-Related Adverse Events^a

DRUG	CONCENTRATION	TYPE OF PREPARATION ^b	PROPOSED DAILY DOSE ^d	AVAILABLE COMMERCIALLY IN THE US	COMMENT
Dexamethasone	0.1 mg/mL (0.01%)	Solution	10 mL 3-6 × d	Yes	Available as an elixir or as an alcohol-free solution
Dexamethasone	0.4 mg/mL (0.04%)	Solution	10 mL 3-6 × d	No	
Prednisolone	3 mg/mL (0.3%)	Solution	5 mL 3-6 × d	Yes	
Budesonide	0.3 mg/mL (0.03%)	Solution	10 mL 2-4 × d	No	
Clobetasol	0.5 mg/mL (0.05%)	Solution	5 mL 3 × d	No	The low bioavailability provides a broader therapeutic range (ie, a longer rinse poses a smaller risk for systemic adverse events compared with other steroid rinses)
Triamcinolone	10 mg/mL (1%)	Solution	5 mL 3-6 × d	No	
Betamethasone	0.5 mg/mL (0.05%)	Solution	10 mL 3-4 × d	No	
Clobetasol	0.05%	Cream, gel	2 × d	Yes	
Triamcinolone	0.1%	Cream, dental paste ^c	2 × d	Yes	The dental paste's semisolid consistency may limit its use on friction-bearing oral soft surfaces
Triamcinolone	0.5%	Cream	2 × d	Yes	
Halobetasol	0.05%	Cream	2 × d	Yes	Limited information about flavor acceptance
Betamethasone	0.05%	Cream, gel, ointment	2 × d	Yes	Limited information about flavor acceptance
Betamethasone	0.1%	Cream, ointment	2 × d	Yes	Limited information about flavor acceptance
Fluocinonide	0.05%	Gel	2 × d	Yes	

^aModified from: Elad S, Zinchuk K, Li S, Cutler C, Liesveld J, Treister NS. Economic and practical considerations in the treatment of oral mucosal chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2018;24:1748-1753.⁸⁷

^bApplying a topical steroid over a large oral surface on a regular basis may increase the risk for oral candidiasis. In patients with a history of repeated oral candidiasis, anti-*Candida* prophylaxis may be needed.

^cThe dental paste is the only steroid preparation that is cleared for topical oral use by the US Food and Drug Administration; the remaining commercially available topical agents are prescribed off-label.

^dOral solutions are administered topically (swish and spit).



FIGURE 8. Oral Mucosal Immune-Related Adverse Event. Ulcerative mucositis in a patient aged 15 years treated with pembrolizumab for anaplastic astrocytoma.

(CTLA4), PD-1, and PD-L1. Anti-CTLA-4 and anti-PD-1/PD-L1 agents share a similar, broad spectrum of toxicities. However, treatment with ipilimumab, an anti-CTLA-4 agent, is associated with greater frequency and severity of irAEs compared with anti-PD-1/PD-L1 agents.^{105–107}

Outcome Assessment Measures

Assessed using the NCI-CTCAE scale (see Outcome Assessment Measures, above), the spectrum of irAEs in randomized trials is generally low-grade and well tolerated, especially with single-agent immune checkpoint inhibition.^{108–110} A grading system for irAEs was proposed recently.¹¹¹ Of note, the NCI-CTCAE scale and the recently proposed scale only address erythema and ulceration and do not address the typical lichenoid presentation. Therefore, the NCI-CTCAE scale may not accurately reflect the extent and severity of OM-irAEs.

Management

Because current experience with OM-irAEs is limited, management recommendations are based on expert opinion and follow regimens for other immune mucosal conditions.^{77,107,112} The unpredictable onset of irAEs highlights the importance of oral examinations with long-term monitoring, even after termination of treatment. For new oral

ulcerative irAEs, a workup according to the differential diagnosis should be performed. Occasionally, tests, such as a biopsy to assess for vesiculobullous diseases, a swab to assess for viral or bacterial infection, or a blood test to rule out leukopenia or neutropenia, may be needed.

The main treatment goal is to reduce the oral lesions-related symptoms. For this goal, OM-irAEs may respond well to topical corticosteroid therapy. However, depending on the severity, systemic corticosteroids and discontinuation of immunotherapy may be required.^{77,94} However, the use of systemic corticosteroids for irAEs may blunt the therapeutic response to an ICI, ie, reduce its effectiveness. Therefore, topical treatment is considered ideal for oral irAEs. Although the evidence in oral irAEs is very limited, selection of the type and preparation of the topical steroid are based on evidence in other oral inflammatory mucosal conditions. The commonly used topical steroids include dexamethasone, clobetasol, betamethasone, fluocinonide, and triamcinolone (Table 3).^{87,111} Gel preparations are applied directly to the affected buccal, labial, and tongue mucosa, whereas steroid solutions are used as swish-and-spit preparations. Intralesional injections of triamcinolone acetonide also may be helpful for resistant oral irAEs.

Mucositis Interventions Under Development

OM remains a significant unmet clinical need. Fortunately, as understanding of mucositis' pathobiology has evolved, so has the identity of potential druggable targets to impair its development.¹¹³ Simultaneously, data have emerged confirming that differences in tumor and normal cell behavior provided a window previously not appreciated in which normal cells could be protected independent of tumor cell susceptibility to cancer treatment. Thus a surge of pharmaceutical industry interest has spurred the development of small molecules for mucositis interventions. Aside from the unmet clinical need, this interest has been catalyzed by the expanding mucositis market and, given the pathobiological commonalities of regimen-related toxicities, a successful mucositis intervention is likely to open a series of halo indications, including chemotherapy-associated or radiation-associated injury to the rest of the gastrointestinal tract, especially the esophagus and rectum, and to the skin and lung. Of the compounds currently in middle-stage to late-stage clinical development, oxidative stress, the innate immune response, the inflammatory response, and wound healing have been the primary mechanistic targets.

The majority of interventional, pharma-sponsored trials are focused on mucositis associated with concomitant CRT regimens for selected H&N cancers. To assure equivalent OM risk across patients, trials typically mandate the tissues to be included in radiation fields, the radiation fraction size

(usually 2 Gy daily), and an independent radiation therapy quality review. For studies in which mitigation of OM is the primary efficacy end point, WHO criteria for mucositis severity have been the gold standard. An advantage of the CRT H&N cancer study population is the requirement for daily (during the week) presence in the clinic to receive radiation, which facilitates in-person interaction with study staff and enhances diary compliance and oral hygiene instruction and reinforcement. Clinical assessments are generally performed twice weekly. In all cases, assuring that the clinical assessors have been thoroughly trained and are validated has increased the consistency of assessments and interobserver concordance. The choice of CRT-associated mucositis as a primary outcome is likely associated with the overall frequency of severe mucositis (range, 60%–70%) in these patients, the increasing number of patients with H&N cancer (>600,000 new cases annually worldwide), the extended mucositis at-risk period because of typical 7-week fractionated radiation dosing regimens, and the extent of the health and economic incremental costs attributable to OM.

As noted above, oxidative stress is a major component in the initiation and prolongation of regimen-related mucositis. The therapeutic potential of small-molecule supplementation of naturally occurring antioxidant enzymes to effectively mitigate radiation injury is currently under clinical development. Avasopasem manganese (GC4419) is a superoxide dismutase mimetic being developed by Galera Therapeutics for OM in patients receiving concomitant CRT for cancers of the mouth and oropharynx. The results of a phase 2 trial (ClinicalTrials.gov identifier NCT02508389),¹⁰ in which patients received study drug by intravenous infusion immediately before each radiation dose, demonstrated significant reductions in both the incidence (65% vs 43% for placebo vs 90 mg of GC4419; $P < .009$) and duration (19 vs 1.5 days for placebo vs 90 mg of GC4419; $P < .024$) of SOM in patients receiving 90 mg GC4419 compared with individuals in the placebo cohort. There were no significant AEs associated with the study drug. A phase 3 trial of 450 patients (2:1 randomization scheme active vs placebo) undergoing concomitant CRT for oral and oropharyngeal cancer (ClinicalTrials.gov identifier NCT03689712) is planned to be completed by late 2021.

A different approach to reducing oxidative stress targets the Nrf2 transcription factor, which, when activated, stimulates antioxidant enzymes such as glutathione-S-transferase and thioreductase 1,¹¹⁴ and thereby reduces the effects of radiation-induced oxidative stress. Both Supportive Therapeutics (ST-617) and Prothex (Rx001) have used this approach as a prophylactic intervention for patients being treated with CRT for cancers of the H&N. ST-617 is delivered in a daily swish-and-swallow formulation, beginning before CRT and continuing throughout the radiation period. In contrast, Rx001 is given by infusion after mixing

the drug with the patient's red blood cells (ClinicalTrials.gov identifier NCT03515538). Results of both formulations appear promising, in that both favorably affected the severity and course of SOM.¹¹³

MitoImmune is about to initiate a small phase 2 dose-ranging trial of their agent MIT-101 (ClinicalTrials.gov identifier NCT04651634). MIT-101 is a mitochondria-targeted antioxidant that is thought to exert its effect by targeting DAMPs to prevent downstream oxidative stress and inflammatory mechanisms.

Given its importance in the initiation of radiation-induced tissue injury, the innate immune response is a rational biological target for potential antimucositis molecules. EC-18 is a small, synthetically produced molecule (1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol) that replicates a known biologically active agent derived from the horns of silk deer. Being developed by Enzychem Lifesciences, the results of a phase 2 trial (ClinicalTrials.gov identifier NCT03200340), in which the compound is delivered as a twice-daily capsule during the CRT period, should be available in late 2021.

An alternative approach was taken by Innovation Pharmaceuticals, which tested their defensin mimetic, Brilacidin, in a small phase 2 trial (ClinicalTrials.gov identifier NCT02324335). Data from the study completed in 2018 showed that Brilacidin administered as an oral rinse favorably affected the incidence of SOM by 65% compared with placebo (Brilacidin, 25.0%; placebo, 71.4%; $P = .0480$).^{115,116} Unlike avasopasem manganese, for which efficacy was independent of cisplatin regimen, Brilacidin was more effective in patients being treated when cisplatin was administered triweekly at a high dose (vs weekly at a low dose). No further trials have yet been started or completed.

As noted above, it is well known that NF- κ B–derived cytokines are a destructive force in OM pathogenesis. Monopar Therapeutics is testing the efficacy of a novel, slow-release formulation of clonidine for mucositis in the H&N cancer population (ClinicalTrials.gov identifier NCT04648020). The compound, Validive, was previously shown to affect the course and severity of mucositis when administered as a troche placed between the lip and alveolar mucosa in the region of the maxillary canine. SOM developed in 45% versus 60% of patients ($P = .06$) who received clonidine versus placebo and occurred for the first time at 60 Gy as opposed to 48 Gy (median hazard ratio, 0.75; 95% CI, 0.484–1.175; $P = .21$), and the median time to onset was 45 versus 36 days. The safety profile of the study drug was similar to that of placebo.¹¹⁷

Mucositis and Health Economics

In addition to its symptomatic impact, OM poses a significant health economic burden because its presence is

associated with increased rates of hospital admission, length of hospital stay, emergency department visits, number of clinic visits, nutritional consult visits, increased supplemental feeding options, and opioids and antibiotic use.⁹

The cumulative cost of this increased resource consumption is significant. The incremental cost of OM ranged from approximately \$5000 to \$30,000 among patients receiving RT and was \$3700 per cycle among patients receiving chemotherapy. The incremental cost of OM-related hospitalization among stem cell transplant recipients exceeded \$70,000.¹¹⁸ Of note, these studies calculated the cost of OM in the immediate term after cancer therapy. Inflating the costs for the current equivalent currency, the cost of OM in patients receiving RT to the H&N is >\$8000, in HCT recipients it is >\$73,000, and it is much higher in patients with SOM.¹¹⁸

Because some patients undergoing RT to the H&N may develop chronic OM, the costs of long-term treatment for OM may continue after cancer therapy finishes. The costs of OM-irAE and OMT have not been studied yet.

In countries where PBM therapy is widely used, the current literature suggests a financial advantage of using it to prevent OM.¹¹⁹ This cost-effectiveness analysis may not apply universally. Of relevance, third-party reimbursement

for most palliative devices, such as PBM therapy, is lacking in the United States.

Conclusion

OM is a common and debilitating complication of cancer therapy. The supportive care for OM has been studied extensively, but evidence-based interventions are limited to certain cancer therapy settings and are not universally available. The improvements in our understanding of its pathogenesis should facilitate the discovery of mechanistic-based interventions. Simultaneously, with the proliferation of targeted therapies and immunotherapies, reports on OMTs and OM-irAEs are increasing. Therefore, the needs and opportunities for developing effective, personalized mucositis interventions are likely to grow and remain for the foreseeable future. Clinicians involved in the management of OM tend to belong to multidisciplinary teams, and the medical and emotional support given to these patients is essential to the success of their cancer treatment. ■

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