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Oral mucositis

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Oral mucositis (OM) refers to erythematous, erosive, and ulcerative lesions of the oral mucosa seen in two patient populations: (1) head and neck cancer patients undergoing radiation therapy (RT) to fields involving the oral cavity; (2) patients receiving high-dose chemotherapy for cancer, including those receiving myeloablative chemotherapy as conditioning for hematopoietic stem cell transplantation.

Most head and neck cancer patients are treated with RT, often in combination with surgery or chemotherapy. OM occurs in 97% of head and neck cancer patients receiving conventional fractionated RT (one dose/day, 5 days/week for 5–7 weeks) and in 100% of patients receiving altered fractionation RT (two or more doses/day). Severe OM develops in 34% of patients receiving conventional RT and in more than 56% of patients receiving altered fractionation RT to the head and neck region [1]. These ulcerative lesions are typically severely painful and compromise nutritional intake and overall quality of life. The severe pain often necessitates the use of systemic opioid analgesics. Patients with severe OM have great difficulty in swallowing and may need nutrition through gastric tube or intravenous line. Sixteen percent of patients receiving RT for head and neck cancer require hospitalization because of mucositis [1]. Furthermore, the

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ulcerations of OM often become secondarily infected and can serve as portals of systemic infection, particularly in patients who are immunosuppressed because of concomitant chemotherapy. Although some centers plan treatment breaks because of severe mucositis, severe mucositis necessitates unplanned interruptions in RT in approximately 11% of patients, thereby compromising cancer treatment and patient survival [1]. Thus, the literature defines OM as the major dose-limiting toxicity of RT to the head and neck region. In addition, RT-induced OM has a significant economic impact due to costs associated with opioid therapy, liquid diet supplements, gastric tube placement or total parenteral nutrition, hospitalizations, and prophylaxis or treatment of secondary infections.

OM also is a significant complication of high-dose chemotherapy in cancer patients. In a recent study of patients undergoing chemotherapy for solid tumors or lymphomas, 303 of 599 patients (more than 50%) developed oral or gastrointestinal (GI) mucositis. OM developed during 22% of 1236 cycles of chemotherapy, GI mucositis developed during 7% of cycles, and both oral and GI mucositis developed during 8% of cycles [2]. The risk of infection in these immunosuppressed patients was significantly (more than twofold) higher during cycles with mucositis than during cycles without mucositis even though the level and duration of neutropenia was similar. The risk of infection increased with increasing severity of mucositis. Infection-related deaths were significantly more common during cycles with both OM and GI mucositis [2]. During chemotherapy cycles with mucositis, the average duration of hospitalization was significantly longer. The use of liquid diets, total parenteral nutrition, fluid replacement, and antifungal or antiviral prophylaxis or therapy was more common in cycles with mucositis. It was estimated that the cost of hospitalization was $3893/chemotherapy cycle without mucositis, $6277/cycle with OM, and $9132/cycle with both OM and GI mucositis. Perhaps most importantly, a reduction in the next dose of chemotherapy was twice as common after cycles with mucositis than after cycles without mucositis [2]. This finding confirms the role of OM as a dose-limiting toxicity of cancer chemotherapy with direct effects on patient survival.

OM is an especially severe problem in patients who receive high-dose myeloablative chemotherapy as conditioning for hematopoietic stem cell transplantation, affecting approximately 80% of this population [3]. In these patients, OM commonly necessitates the use of systemic opioid analgesics and total parenteral nutrition. From the patient's point of view, OM often is the single most debilitating complication of a transplantation [4]. Because these patients are typically severely immunosuppressed, infections of the oral lesions have resulted in life-threatening systemic sepsis during myeloablation [5]. Moderate to severe OM has been correlated with blood infections and transplantation-related mortality [6]. A single-point increase in peak mucositis scores in stem cell transplant patients is associated with 1 additional day of fever, a 2.1-fold increase in risk of significant infection, 2.7 additional days of total parenteral nutrition, 2.6 additional days of injectable narcotic

therapy, 2.6 additional days in hospital, $25,405 in additional hospital charges and a 3.9-fold increase in 100-day mortality risk [7].

Thus, OM is a significant and dose-limiting toxicity of cancer therapy, with important clinical and economic implications. This article reviews the current knowledge on the pathogenesis, clinical presentation, diagnosis, and management of OM.

Pathogenesis

Historically, OM was thought to result solely from the direct toxic effects of RT or chemotherapy on the stem cells in the basal and suprabasal layers of the oral epithelium. These rapidly dividing cells are responsible for the normal renewal and repopulation of the oral epithelium. Therefore, damage to these cells leads to atrophy and ulceration of the oral mucosa, as seen in mucositis. Mouse studies have demonstrated that high-dose radiation leads to loss of the normal structure of basal cells of the tongue epithelium with many fragmented nuclei [8]. Furthermore, daily fractionated radiation leads to significant decreases in proliferative activity and cellularity of mouse-tongue epithelium [9]. Similarly, treatment of rats with the chemotherapeutic agent 5-fluorouracil (5-FU) causes DNA strand breaks, vacuolation, and degeneration of basal epithelial cells of the buccal mucosa [10]. Human oral mucosa examined by transmission electron microscopy following systemic chemotherapy demonstrates increased vacuolation within cytoplasm of basal cells, loss of membrane contact with neighboring cells, multinucleation of suprabasal cells, and increased apoptosis [11]. Although this direct pathway of mucosal injury undoubtedly plays a role in the pathogenesis of OM, studies have indicated that the mechanisms involved are much more complex. The turnover time of nonkeratinized human oral epithelium (in the buccal mucosa) is approximately 14 days [12]; however, clinical mucosal ulceration can be first seen as early as 7 to 10 days after toxic levels of cancer therapy are delivered. Therefore, factors other than direct injury may be contributing to acceleration and aggravation of oral mucosal injury.

In 1998, Sonis [13] proposed a four-stage model for the pathogenesis of OM. This model was revised in 2004 by Sonis and colleagues [14] to include the following five stages:

1. Initiation of tissue injury: It has been hypothesized that the generation of reactive oxygen species by RT or chemotherapy plays a role in the initiation of mucosal injury.
2. Increased injury through the generation of messenger signals: In addition to causing direct cell death, RT or chemotherapy could also induce activation of second messengers such as ceramide or transcription factors such as nuclear factor-kappa B. Collectively, activation of these molecules would lead to increased expression of proinflammatory cytokines, tissue injury, and cell death.

3. Signaling and amplification: Increased expression of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), in addition to direct injurious effects on mucosal cells, could also result in activation of other pathways that would amplify mucosal injury.
4. Ulceration with inflammation: During the ulcerative phase of mucositis, there is a significant inflammatory cell infiltrate in the affected tissue. There is a further increase in the production of proinflammatory cytokines [15]. The ulcers are colonized by oral bacteria.
5. Healing: There is a renewal of epithelial proliferation and differentiation leading to healing of the affected tissue [9].

Several aspects of this model are supported by the available evidence. It has recently been reported that inhibition of ceramide synthase attenuates RT-induced OM in hamsters [16]. A number of studies support a role for proinflammatory cytokines in the pathogenesis of OM. Administration of RT and chemotherapy has been demonstrated to cause significant elevations in the release of proinflammatory cytokines including TNF-α, interleukin-1 alpha (IL-1α), and interleukin-6 (IL-6) from several different tissues [17,18]. In a hamster cheek pouch model of radiation mucositis, mRNA levels of TNF-α and IL-1β in oral mucosal tissue correlated with severity of mucosal injury. Furthermore, animals treated with the anti-inflammatory cytokine interleukin-11 (IL-11) demonstrated a significant reduction in mucosal injury accompanied by reduced levels of TNF-α and IL-1β [15]. Both TNF-α and IL-1β induce the expression of cyclo-oxygenase-2 (COX-2), which is a key enzyme involved in the inflammatory process [19]. COX-2 expression is increased in irradiated hamster oral mucosa and is highest during peak mucositis severity [20]. COX-2 mediates the increased production of proinflammatory prostanoids at sites of inflammation. These prostanoids include prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2), both of which are known to play critical roles in the pain response by acting at prostaglandin receptors on neurons [21]. Further evidence for a role for proinflammatory cytokines comes from the relative success of anti-inflammatory agents in reducing the severity of OM lesions (as discussed later in this article).

It has been suggested that bacterial colonization of OM ulcerations could further increase tissue injury by amplifying the inflammatory response. It is known that bacterial products can induce the release of proinflammatory cytokines; for example, bacterial lipopolysaccharides can induce TNF-α release [22]. However, as discussed later in this article studies using antimicrobial agents in OM have yielded mostly negative results.

Clinical presentation

OM typically begins as erythema of the oral mucosa, which may or may not be symptomatic. In some but not all patients, this erythema is followed

by frank ulceration of the affected tissue. The ulcerations may be covered by a white pseudomembrane (Fig. 1). The ulcerative stage is typically painful and affects nutritional intake and quality of life. The lesions heal within approximately 2 to 4 weeks after the last dose of stomatotoxic therapy has been delivered.

The onset, location, and severity of oral lesions vary based on the stomatotoxic therapy being delivered. In chemotherapy-induced OM, lesions are usually limited to nonkeratinized areas. The lateral and ventral tongue, buccal mucosa, and soft palate are commonly affected sites. Ulceration occurs approximately 1 to 2 weeks after stomatotoxic levels of chemotherapy have been delivered. Severity of oral lesions is directly affected by type and dose of chemotherapeutic agent used. Antimetabolites and alkylating agents have been reported to cause a high incidence and severity of OM [23].

In RT-induced OM (Fig. 2), lesions are limited to the tissues in the field of radiation, with nonkeratinized tissues affected more often. Typically, RT for head and neck cancer is delivered in fractions of approximately 2 Gy/day, 5 days/week, for a total dose of 50 to 70 Gy over 5 to 7 weeks. Signs of mucositis may be first seen after approximately 30 Gy has been delivered (at the end of week 3). Severity of oral lesions increases with increasing dose of RT. Almost all patients who have received more than 50 Gy to the oral mucosa develop ulcerative OM [24]. The use of midline radiation blocks and advanced radiation delivery techniques, such as intensity-modulated radiotherapy, reduces the radiation dose to nontarget tissues and reduces the severity or extent of OM [25,26].

In addition to nature of stomatotoxic therapy, several other factors may also affect the risk for OM. Improving oral hygiene has been reported to result in reduced incidence and severity of OM [27–29]. There are conflicting reports on the effects of age, gender, and nutritional status on the risk for OM [23]. It also has been suggested that there may be genetic influences on the risk for OM [14].

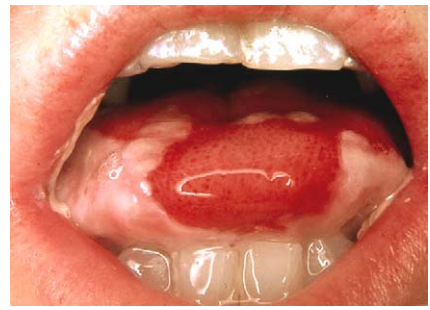

Fig. 1. Chemotherapy-induced oral mucositis seen 10 days after high-dose chemotherapy including 5-fluorouracil.

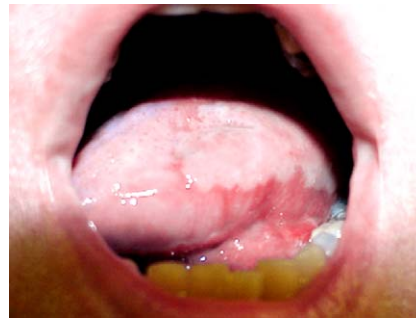

Fig. 2. Radiation-induced oral mucositis in a patient who has received 46-Gy radiation therapy for treatment of a squamous cell carcinoma of the oropharynx and tonsillar region.

Diagnosis

OM is diagnosed clinically based on:

Clinical appearance: OM typically begins as erythema of the oral mucosa, followed by ulceration that may be covered by a white pseudomembrane.

Symptoms: Lesions are typically painful and compromise nutritional intake.

History of stomatotoxic therapy: Either systemic chemotherapy or RT to fields including the oral cavity can cause OM.

Timing of onset of lesions: Lesions typically occur 1 to 2 weeks after stomatotoxic levels of chemotherapy have been delivered or after more than 30 Gy of RT have been delivered.

Duration of lesions: Lesions usually heal within approximately 2 to 4 weeks after the last dose of stomatotoxic therapy has been delivered.

Location of lesions: Lesions are usually limited to nonkeratinized tissues; RT-induced OM is limited to areas in the field of radiation.

The clinical course of OM may sometimes be complicated by local infection. In patients who are immunosuppressed because of high-dose chemotherapy, viral and fungal infections can complicate the diagnosis of OM. The most common viral infection seen is recurrent herpes simplex virus (HSV) infection. The clinical presentation of recurrent HSV infection in immunocompromised patients can be much more severe than in immunocompetent patients. Lesions may be extensive and confluent, clinically similar to primary herpetic stomatitis [3]. Therefore, recurrent HSV in chemotherapy patients (Fig. 3) can complicate or be confused with chemotherapy-induced OM. Less commonly, cytomegalovirus may be found in oral lesions in immunocompromised patients [30]. Clinical presentation is nonspecific and can be similar to lesions of OM [31]. If the appearance, onset, duration, or location of oral lesions is inconsistent with OM, viral infection should be suspected, and oral lesions should be cultured.

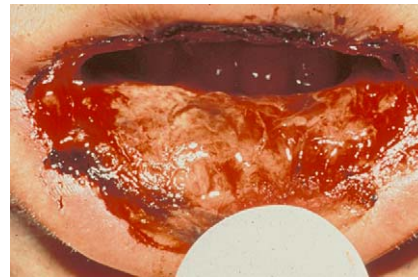

Fig. 3. Recurrent herpes simplex virus infection complicating oral mucositis secondary to conditioning chemotherapy for an allogeneic stem cell transplantation. (Courtesy of Mark M. Schubert, DDS, MSD, Seattle, WA.)

Systemic antiviral therapy with acyclovir often is used for prophylaxis or treatment of oral viral infections in immunocompromised patients.

Oral candidiasis is the most common oral fungal infection seen in immunocompromised patients. The clinical appearance is typically similar to that seen in immunocompetent patients. However, topical antifungal agents may not be effective in treating oral candidiasis in immunocompromised patients. Systemic antifungal therapy with fluconazole is significantly more effective than nystatin in the treatment of oral candidiasis in immunocompromised patients [32]. Oral candidiasis also may complicate OM in patients receiving head and neck RT. In this setting, candidiasis occurs secondary to xerostomia caused by radiation damage to salivary glands. Because these patients are usually not severely immunosuppressed, topical antifungal agents such as nystatin or clotrimazole can be effective.

Patients who have received a hematopoietic stem cell transplant from another individual are at risk for graft-versus-host disease (GVHD). In GVHD, immunocompetent cells introduced with a graft mount an inflammatory response against tissues in an immunocompromised host. The presentation of acute GVHD may include oral mucosal erythema and ulceration [33]. Acute GVHD can occur as early as 10 days after transplantation, which is within 2 to 3 weeks of the pretransplantation high-dose conditioning chemotherapy. Therefore, acute oral GVHD (Fig. 4) can complicate or be confused with chemotherapy-induced OM. In most cases, however, oral GVHD is accompanied by erythematous macules or papules on the skin. A definitive diagnosis of oral GVHD can be established by demonstration of a lymphocytic infiltrate and epithelial cell necrosis on biopsy [3]. Treatment for oral GVHD includes topical and/or systemic steroids or systemic immunosuppressants.

Measurement

A number of subjective and objective scales have been used to measure OM. The measurement of the severity of OM can be used to determine

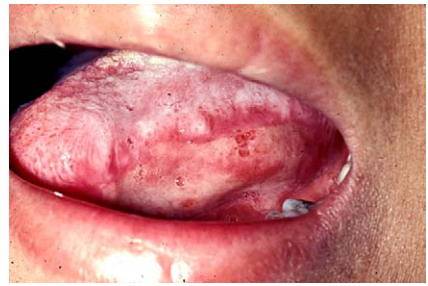

Fig. 4. Acute oral graft-versus-host disease seen 35 days after an allogeneic stem cell transplantation from a matched sibling donor. (Courtesy of Mark M. Schubert, DDS, MSD, Seattle, WA.)

disease status and assign or evaluate therapy in clinical care. The World Health Organization (WHO) scale is a simple five-point scale that combines subjective and objective measures of OM (Box 1).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Box 2) includes separate subjective and objective scales for OM [34].

Accurate measurement of OM severity is also required in research protocols that are either measuring the toxicity of a particular cancer-therapy regimen or evaluating the efficacy of an intervention to prevent or reduce the severity of OM. The Oral Mucositis Assessment Scale is an objective scale that measures erythema and ulceration at nine different sites in the oral cavity. This scale was validated in a multicenter trial with high interobserver reproducibility and strong correlation of objective mucositis scores with patient symptoms [35].

Management

Mouth care

As discussed earlier, maintenance of good oral hygiene has been reported to result in reduced incidence and severity of OM [27–29]. Therefore, an

Box 1. WHO scale for oral mucositis

Grade 0 No oral mucositis
Grade 1 Erythema and soreness
Grade 2 Ulcers, able to eat solids
Grade 3 Ulcers, requires liquid diet because of mucositis
Grade 4 Ulcers, alimentation not possible because of mucositis

Box 2. National Cancer Institute common terminology criteria for adverse events (CTCAE) version 3.0

Oral mucositis (findings on clinical examination)
Grade 1 Erythema of the mucosa
Grade 2 Patchy ulcerations or pseudomembranes
Grade 3 Confluent ulcerations or pseudomembranes; bleeding with minor trauma
Grade 4 Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Grade 5 Death

Oral mucositis (functional/symptomatic effects)
Grade 1 Minimal symptoms, normal diet
Grade 2 Symptomatic but can eat and swallow modified diet
Grade 3 Symptomatic and unable to aliment or hydrate orally adequately
Grade 4 Symptoms associated with life-threatening consequences
Grade 5 Death

oral-care protocol is an important part of OM management. Clinical practice guidelines for OM developed by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) include a suggestion that oral-care protocols that include patient education be used in an attempt to reduce severity of OM [36]. A recent survey (Gerry Barker, RDH, MA, Kansas City, MO, personal communication, June 2003) found that most oral care protocols in cancer patients include:

Dental prophylaxis (cleaning) before cancer therapy, if possible

Twice daily toothbrushing with a soft-bristled toothbrush and fluoride-containing toothpaste. Prescription-strength fluoride toothpastes may be used in patients at increased risk for dental caries secondary to xerostomia.

Flossing, unless contraindicated by low platelet or neutrophil count. Many centers recommend that patients discontinue flossing if they have fewer than 20,000 to 50,000 platelets/mm^3 or fewer than 500 to 1000 neutrophils/mm^3. In such patients, the use of a regular toothbrush may be replaced by an ultrasoft toothbrush or toothette (sponge on a stick).

Rinsing with a nonirritating solution such as saline or 2 tablespoons of sodium bicarbonate (baking soda) in 1 quart of drinking water. In addition to maintaining oral hygiene, rinsing may help decrease

viscosity of saliva. Reducing saliva viscosity is useful in RT-induced salivary hypofunction, since secretion of the serous component of saliva is especially impaired in this condition.

Limiting the use of removable dentures as far as possible to minimize trauma to the oral tissues and decrease risk of infection

Pain control

OM causes significant pain in most patients. This pain adversely affects nutritional intake, mouth care, and quality of life. Therefore, palliation of mucositis pain is a critical component of the management strategy for these patients. Some patients may benefit from the use of topical anesthetics such as viscous lidocaine. Some centers use a combination of lidocaine and a coating agent such as magnesium hydroxide and aluminum hydroxide (Maalox, Aventis Pharmaceuticals, Bridgewater, New Jersey), with or without diphenhydramine (Benadryl, Pfizer Inc., New York, New York). These combinations are sometimes referred to as ''miracle mouthwash'' or ''magic mouthwash.'' These topical formulations provide only short-term relief, however, and are most useful when used before mouthcare. The use of topical anesthetics before meals may be risky because impairment of the swallowing reflex can lead to food aspiration. Gelclair (OSI Pharmaceuticals, Mellville, New York) is a concentrated oral gel that contains adherent, film-forming, and lubricating agents. It is hypothesized to coat exposed nerve endings and thereby reduce pain from oral lesions. In a noncontrolled, open-label study, Gelclair significantly reduced pain scores in 30 persons with mucositis, severe aphthous ulcers, or pain from oral surgery [37]. This product has not yet been tested in controlled clinical trials. Regardless of the use of topical agents, systemic analgesics are needed to achieve satisfactory pain control in most patients with OM. Although nonopioids should be considered first, many patients need opioid analgesics such as oxycodone. The use of opioid analgesics commonly causes nausea, somnolence, and constipation and can, rarely, cause respiratory depression and arrest. In hospitalized patients, patient-controlled analgesia using morphine has been found to be effective [38,39]. The MASCC/ISOO guidelines recommend patient-controlled analgesia with morphine for patients undergoing stem cell transplantation [36].

Nutritional support

Severe OM significantly affects nutritional intake, primarily because of pain. In addition, taste changes have also been reported secondary to both chemotherapy and RT and further affect oral feeding [3]. Patients should be encouraged to ingest soft, nonirritating foods or liquid diet supplements. Patients should be weighed regularly to monitor weight loss. A significant proportion of patients are not able to maintain adequate nutrition by mouth and require feeding by gastric tube or intravenous line. A dietician and the patient's caregivers should be involved in maintaining nutritional support.

Targeted therapeutic interventions

Because of the significant clinical and economic impact of OM, there has been a substantial increase in clinical research in this area during the past decade. Although the Food and Drug Administration (FDA) has not approved any drugs for this indication to date, there are several promising candidates in various stages of development. The following sections summarize the current clinical knowledge on interventions to prevent or reduce the severity of OM.

Growth factors

As discussed earlier, cancer therapy-induced damage to the proliferative capacity of the oral epithelium is thought to play a role in the pathogenesis of OM. Therefore there has been interest in studying the use of growth factors to stimulate the proliferation of epithelial cells. Intravenous recombinant human keratinocyte growth factor-1 (rHuKGF-1) was evaluated in a phase III, randomized, double-blind, placebo-controlled trial in patients with hematologic malignancies receiving high-dose chemotherapy and total body irradiation before autologous peripheral blood progenitor cell transplantation. RHuKGF-1 was found to reduce the duration and incidence of severe OM significantly as compared with placebo [40]. On the other hand, a double-blind, crossover, phase II trial of human keratinocyte growth factor-2 (KGF-2) found no significant difference between the KGF-2 and placebo groups in the percentage of subjects who experienced severe mucositis [41]. There is a theoretic concern that epithelial growth factors could also promote proliferation of tumor cells. Although results from a phase II trial in advanced colorectal cancer indicated no difference in median survival between 28 subjects who received rHuKGF-1 and 36 subjects who received placebo [42], additional long-term data are required to address this concern satisfactorily.

Several clinical studies have examined the use of granulocyte-macrophage colony stimulating factor (GM-CSF) or granulocyte-colony stimulating factor (G-CSF) in OM. GM-CSF stimulates the formation of granulocytes and macrophages and has also been found to stimulate proliferation of endothelial cells [43]. The mechanisms whereby GM-CSF and related factors could affect OM are not understood, however. The Cochrane Oral Health Group conducted a systematic review of seven clinical trials that compared GM-CSF or G-CSF with a placebo or no-treatment group in chemotherapy- or RT-induced OM. They found that there is moderate evidence that G-CSF may prevent OM and no evidence that G-CSF or GM-CSF reduces the severity of OM [44].

Anti-inflammatory agents

Given the evidence supporting a role for proinflammatory cytokines in OM, a wide variety of anti-inflammatory agents have been tested for their

ability to ameliorate this condition. Benzydamine hydrochloride is a nonsteroidal drug that is known to have anti-inflammatory properties. Benzydamine inhibits production of proinflammatory cytokines, including TNF-α, from human mononuclear phagocytes [45]. A multicenter, randomized, double-blind, placebo-controlled clinical trial was performed to evaluate the effectiveness of benzydamine in RT-induced OM. Up to cumulative doses of 50 Gy, patients receiving benzydamine mouthrinse had significantly less erythema and ulceration and were more likely to remain ulcer-free than patients receiving placebo mouthrinse [46]. The MASCC/ISOO guidelines recommend benzydamine for prevention of RT-induced OM in patients receiving moderate-dose RT [36]. The FDA has not approved this agent, however; furthermore, most head and neck cancer patients receive doses greater than 50 Gy. A phase III clinical trial of benzydamine in RT-induced OM is currently in progress. Corticosteroids and nonsteroidal anti-inflammatory agents have also been studied as interventions for OM. An uncontrolled study in five persons receiving 60 Gy to the oral cavity reported complete prevention of RT-induced OM using a betamethasone mouthrinse [47]. It has been anecdotally reported that a short course of systemic prednisone has been helpful in reducing inflammation and discomfort in RT-induced OM [48]. A randomized, double-blind, placebo-controlled study of systemic prednisone versus placebo in RT-induced OM found a trend favoring shorter treatment interruptions in the prednisone arm but not a reduction in the intensity or duration of mucositis [49]. A double-blind, placebo-controlled study found that subjects given indomethacin had milder irradiation esophagitis (by endoscopy) and symptomatology than controls [50]. In another clinical study, systemic indomethacin administration was found to delay onset of severe OM secondary to RT as compared with patients receiving placebo [51].

Antimicrobial agents

As mentioned earlier, it has been hypothesized that microbial colonization of OM lesions worsens their severity. Although there is no direct evidence to support this hypothesis, a number of antimicrobial agents have been evaluated in OM. Several trials have studied the effects of chlorhexidine gluconate mouthrinse on OM. The Cochrane Oral Health group performed a meta-analysis of six trials comparing chlorhexidine with placebo or no treatment. They concluded that there is no evidence that chlorhexidine has any benefit in preventing or reducing severity of OM [44]. Similarly, the MASCC/ISOO guidelines recommend that chlorhexidine not be used to prevent or treat OM [36]. Although one study [52] reported a reduction in severity of RT-induced OM using antibiotic pastilles containing polymyxin, tobramycin, and amphotericin, another study found no benefit using a paste with the same agents [53]. A double-blind, placebo-controlled trial found that systemic acyclovir therapy caused no difference in

the frequency or duration of chemotherapy- or RT-induced oral lesions [54]. A phase III multicenter, randomized, double-blind, vehicle-controlled study with 355 subjects found that 0.1% triclosan mouthrinse failed to reduce the incidence or duration of OM induced by chemotherapy or total body irradiation [55].

Topical coating agents

It has been hypothesized that agents that topically coat the oral mucosa may protect OM lesions from further injury and thus exert a beneficial effect. Sucralfate suspension has been approved for the short-term treatment of active duodenal ulcers. In that setting, it is believed to act through multiple local mechanisms, including the formation of a protective coating that adheres to the ulcer. An analysis of six trials comparing topical sucralfate with placebo in RT- and chemotherapy-induced OM indicated that there is no evidence that sucralfate is effective in preventing OM [44].

Nutritional supplements

Glutamine is an amino acid that is believed to play a role in wound healing. The Cochrane Oral Health Group conducted a meta-analysis of five trials evaluating topical or systemic glutamine administration in chemotherapy- or RT-induced OM. They found no evidence that glutamine prevents or reduces severity of OM [44]. AES-14 (Aesgen Inc., Princeton, New Jersey) is a proprietary L-glutamine-based oral suspension that has been shown to enhance the uptake of L-glutamine into epithelial cells in vitro. A phase III randomized, double-blind, placebo-controlled trial with 326 subjects found that persons receiving AES-14 had a 22% lower incidence of WHO grade 2 or higher chemotherapy-induced OM than persons receiving placebo ($P = 0.0269$) [56]. Folinic acid is an active form of the folate group of vitamins. The addition of folinic acid to chemotherapy with 5-FU has been reported to increase the severity of OM compared with subjects receiving 5-FU alone [57].

Antioxidants

Amifostine is a prodrug that is dephosphorylated in tissues to a pharmacologically active free thiol metabolite. This thiol metabolite can scavenge reactive oxygen species generated by exposure to radiation. The effects of intravenous amifostine on xerostomia and mucositis secondary to head and neck RT were studied in an open-label phase III trial [58]. There was a significant reduction in the incidence of grade 2 or higher acute and late xerostomia in the amifostine group, as assessed by nonblinded investigators. There was no significant difference in the incidence or severity of mucositis between the two groups. Intravenous amifostine has been approved by the FDA to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative RT for head and neck cancer when the radiation port includes a substantial portion of the parotid

glands. RK-0202 (RxKinetix, Louisville, Colorado) is comprised of the thiol antioxidant *N*-acetylcysteine, formulated in a proprietary matrix for topical application in the oral cavity. A phase II clinical trial of this product in RT-induced OM is currently in progress.

Laser therapy

Three controlled studies have examined the effects of low-energy Helium-Neon laser therapy on OM (two on chemotherapy-induced OM [59,60] and one on RT-induced OM [61]). All three studies found a beneficial effect of the laser therapy on severity and pain of OM. It has been suggested that low-energy laser therapy may positively affect healing of mucositis lesions [61]. The MASCC/ISOO guidelines suggest that low-level laser therapy be used in management of OM in patients receiving high-dose chemotherapy, at centers capable of supporting the necessary technology and training [36].

Cryotherapy

Two randomized, controlled trials have indicated that the placement of ice chips in the mouth for 30 minutes during delivery of a bolus dose of 5-FU reduced severity of OM [62,63]. Two noncontrolled studies reported that cryotherapy also may be beneficial in patients receiving bolus doses of edatrexate [64,65]. The hypothesized mechanism is local vasoconstriction and reduced blood flow, resulting in decreased delivery of the chemotherapeutic agent to the oral mucosa. The MASCC/ISOO guidelines recommend that patients receiving bolus 5-FU undergo 30 minutes oral cryotherapy to prevent OM and suggest the use of 20 to 30 minutes of oral cryotherapy in patients treated with bolus edatrexate [36].

Summary

OM refers to erythematous, erosive, and ulcerative lesions of the oral mucosa seen in two patient populations: (1) head and neck cancer patients undergoing RT to fields involving the oral cavity, and (2) patients receiving high-dose chemotherapy for cancer. OM is a significant and dose-limiting toxicity of cancer therapy, with important clinical and economic implications. OM is diagnosed clinically based on history of stomatotoxic therapy, clinical appearance, symptoms, onset, duration, and location of lesions. Because of the absence of any therapy approved by the FDA, current management of OM is largely palliative. The primary management considerations are maintenance of good oral hygiene, pain control, and nutritional support. Clinical practice guidelines for the management of OM are now available. The dental professional should work closely with the medical providers in the management of OM.

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