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REVIEW ARTICLE

# Oral Radiation Mucositis: A Short Review

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**ABSTRACT**

Oral radiation mucositis is one of the debilitating and dose-limiting acute toxicity during (chemo) radiation or for HNC having a major impact on the patient daily functioning, well-being and quality of life. The unplanned interruption of treatment secondary to mucositis may compromise the treatment and the outcomes if not adequately addressed. Recently, the integrated pathophysiological mechanism of radiation injury has been proposed, aiding development of certain targeted therapies for the prevention and treatment of oral mucositis. Although there are currently no approved agents or strategies that can reliably prevent or treat oral mucositis, there are several agents are under investigation and development. This is an exciting juncture in the development of drugs and drug delivery agents for radiation oral mucositis. This review is to have a peep into currently available options at present to optimally know when these agents can be used and what should be the direction of future research to maximize the therapeutic benefit.

**Keywords:** Mucositis, Oral mucositis, Radiotherapy.

## INTRODUCTION

There are significant added morbidities of the cancer due to its treatment side effects. There are various modalities used, such as surgery, radiation, chemotherapy either alone or in conjugation as per the disease site and stage. There is growing evidence that more and more aggressive regimens using multimodalities or aggressive single modalities will improve local tumor control and survival in cancer treatment.[1] So, better treatment outcomes, come at the expense of increased patient morbidity, notably an increase in severe (grades 3-4) mucositis, affecting over 40% of head and neck cancer patients.[2]

Nearly all (90-97%) patients receiving radiotherapy in the head and neck develop some degree of mucositis.[2] Of these patients treated with radiotherapy with or without chemotherapy, 34 to 43% develop severe mucositis.[3] Due to this, the patient's quality of life is affected, hospital admittance rates are higher, the use of total parenteral nutrition is increased and interruption of treatment is more frequent, all of which compromises tumor control.[4] Severe mucositis causes 9 to 19% of chemotherapy and radiotherapy interruptions jeopardizing radical treatment outcomes.[5,6] The severity of oral mucositis increases in (1) patients with primary tumors in the oral cavity, oropharynx or nasopharynx, (2) treated with concomitant chemotherapy, (3) receiving a total dose over 5000 cGy, and (4) treated with altered fractionation radiation schedules. So, mucositis can be an important dose limiting toxicity compromising curability, while causing significant morbidity during treatment.

### Definition and Clinical Features

Mucositis is an acute injury to the mucosal lining of any site from alimentary canal due to radiation or chemotherapy.[7] In head and neck region, radiation therapy potentially affects any mucosal surface exposed, from lips to cervical esophagus. Use of chemotherapy shortens the duration for appearance and increases the severity of mucositis.

Clinically, mucosal changes range from mild erythema to deep mucosal ulceration.[8] The ulcers are typically covered by exudates composed of cells, serum and debris, so this more advanced stage is interchangeably referred to as 'ulcerative', 'fibrinous' or 'pseudomembranous' mucositis.[7] The pseudomembrane is analogous to an eschar in superficial skin lesion. Pseudomembrane appears white or opaque when hydrated by saliva, and may appear yellowish or greenish due to superficial infection, especially when associated with deep ulcers. Food, milk, beverages or topical medication may also change the color.[9] Careful inspection is necessary to differentiate from candida or viral (HSV) infections.[9] It is a slightly elevated membrane above the level of the underlying mucosa, if the lesion is ulcerated. Mild trauma may remove the membrane, causing bleeding and ulceration. Increased ulcer size results in a wider adjacent pseudomembrane that covers neighboring geographically connected ulcers.

This spectrum of mucosal changes and associated symptom clusters is referred to as radiation-induced mucositis.[10]

The associated symptoms include "mouth and throat sores"; difficulty in swallowing; pain; lost or altered taste

(dysgeusia); excessive mucous secretions associated with dry mouth that may lead to gagging, nausea and vomiting; loss of appetite, fatigue, weight loss and aspiration.[11,12] The excessive viscid mucus associated with xerostomia leading to loss of serous secretions in the mouth, and throat is seldom reported but has been shown to be one of the most burdensome symptoms for many patients with high-grade mucositis.[13,14]

The severity depends on various factors; dose of radiation, dose interval, volume of treated tissue and the type of radiation. The most important being the rate of dose accumulation and the total dose.[15] Other factors are exposure to chemotherapy especially concomitant chemotherapy and systemic diseases, such as diabetes mellitus or vascular conditions compromising mucosal healing.[16] The duration of mucositis is proportional to the degree of mucosal stem cell depletion.[17] It may take weeks to months to heal depending on mucosal stem cell recovery rate. In most patients, healing occurs in two or three weeks after the end of conventionally fractionated radiotherapy. Excessive depletion preventing healing leads to chronic open wound described as "soft tissue necrosis". This is referred as "consequential late effect" of severe acute injury turning to chronic injury.[17,18] Other consequential late effects which can occur due to poor healing or severe acute mucositis are mucosal scarring (healing by secondary intention) and loss of mucosal compliance, adding to chronic dysphagia.

## Measurement of Oral Mucositis

A wide variety of scales have been used to record the extent and severity of oral mucositis in clinical practice and research. The World Health Organization (WHO) scale is simple, easy to use and is suitable for daily use in clinical practice. This scale combines both subjective and objective measures of oral mucositis. The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 3.0 includes separate subjective and objective scales for mucositis. The oral mucositis assessment scale (OMAS) is an objective scale, suitable for research purposes, that measures erythema and ulceration at nine different sites in the oral cavity. This scale has been validated in a multicenter trial with high interobserver reproducibility and strong correlation of objective mucositis scores with patient symptoms.[19] The Eastern Cooperative Oncology Group (ECOG) common toxicity criteria are also used in oncology trials to document severity of oral mucositis.

## Pathophysiology

Dividing cells are sensitive to the effects of anticancer therapy. Cells in the oral mucosa have high mitotic, cell renewal and epithelial maturation rates, and behave as acute reacting tissues showing similar biological response as tumor tissue to radiation.

The mechanisms involved in the pathogenesis of mucositis appear to be much more complex than a direct damage to epithelium theory. Mechanisms for radiation-induced and chemotherapy-induced mucositis are believed to be similar. In 1998, a theoretical model was described for the pathophysiology of radiotherapy-induced mucositis. This model included the interactions of cytokine activity, integrated local immunological and microbacterial effects with the theory of direct and indirect mucosal toxicity.[20]

1. *Initiation of tissue injury*: The biological events starting in submucosa progress towards the epithelium. Radiation and/or chemotherapy causes direct cellular damage by reactive oxygen species (free radicals) resulting in death of the basal epithelial cells.
2. *Upregulation of inflammation via generation of messenger signals*: Free radicals activate second messengers that transmit signals from receptors on the cellular surface to the inside of the cell. This leads to upregulation of proinflammatory cytokines and transcription factors, including interleukin-1 (IL-1) and the tumor necrosis factor-a (TNF-α), mediating local response, followed by apoptosis and cell damage. The chain of biological events in cell and its surroundings presents clinically as visible mucosal ulcers. A fibrin exudate containing cell debris, inflammatory cells, is colonized by bacteria—called the pseudomembrane—covers the ulcer.
3. *Signaling and amplification leading to ulceration and inflammation*: Proinflammatory cytokines and colonizing bacteria penetrating the submucosa, activate macrophages in the infiltrate; producing additional cytokines causing up regulation and amplification of direct and indirect celluar damage. These and other related cytokines cause, dilation of blood vessels and other inflammatory effects, all of which increase the deposition of cytotoxic drugs on the mucosa amplifying mucosal injury. So, this forms a vicious cascade of tissue damage.
4. *Healing*: Characterized by epithelial proliferation, cellular and tissue differentiation, and restoration of the integrity of the epithelium taking around 2 to 3 weeks depending on severity of mucositis. Secondary infection may delay healing of mucosal lesions while larger and deeper ulcers require more time to heal. The profound depletion of mesenchymal cells may result in second intention healing and duration of healing is proportion of mesenchymal cell damage. Depending on the extent of injury, the resulting mucosa may appear pallid, atrophic and less complacent. A few deep ulcers may never heal and may progress to soft tissue necrosis.

During such events, it has been suggested that genetic differences in the inflammatory response may be responsible to variations in susceptibility to oral mucositis and response to further therapy. Recent studies have indicated that

pathways associated with proinflammatory molecules, including cyclo-oxygenase-2, nuclear factor-kappa B and interleukin-6 are upregulated in oral mucositis.[21,22]

## Clinical Management of Oral Mucositis

Currently, there is no drug or intervention approved by Food and Drug Administration (FDA), intervention for the prevention of radiation induced mucositis. Currently, symptomatic treatment is the mainstay of management. Although, targeted therapeutic interventions are now being developed but none is convincingly into common practice. Published recommendations for mucositis interventions include Multinational Association of Supportive Care in Cancer (MASCC),[23] National Comprehensive Cancer Network (NCCN)[24] and Cochrane reviews.[25,26] Accordingly, management of radiation-induced mucositis can be divided into following sections:

| | *Recommendation* | *Comments* |
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| 1. General care | 1. Multidisciplinary approach<br>2. Dental prophylaxis<br>3. Patient and staff education to reduce the severity of oral mucositis<br>4. Regular oral pain and oral cavity health assessment | Development and evaluation of oral care protocols, dental professionals inclusion during treatment and follow-up |
| 2. Pain control | 1. Systemic—Oral narcotics<br>2. Local<br>– Viscous lidocaine<br>– Viscous bupivacaine<br>– Mucopain<br>3. Other agents<br>– Saline mouth rinses<br>– Ice chips<br>– Mucaine gel[27]<br>– Sucralfate[27-29]<br>4. Patient-controlled analgesia with morphine[30] | A. It is the primary symptom of oral mucositis and affects nutritional intake, mouth care and quality of life.<br>B. Most patients need both systemic and topical analgesics.<br>1. Narcotic dose, frequency and duration should be regularly adjusted to meet the intensity level of pain with proper adjuvant therapy to control side effects like vomiting and constipation<br>2. Widely recommended<br>3. a. Wider application and utility, easy, routinely recommended<br>b. For bolus chemotherapy induced only<br>c. Widely recommended as topical analgesia<br>d. Not for radiation mucositis<br>4. Only for hematopoietic stem cell transplantation |
| 3. Nutritional support | 1. Weight monitoring<br>2. Dietician advice<br>3. Soft and liquid diet<br>4. Gastrostomy tube prophylaxis<br>5. Total parenteral nutrition | A. Nutritional intake can be severely compromised due to pain<br>B. Additional taste changes also occur. Practice varies considerably from center to center in hematopoietic cell transplantation |
| 4. Basic oral care | 1. Pretreatment evaluation by dental specialists for restoration or extraction, maintenance of oral hygiene during and after radiation<br>2. Brushing in a nontraumatic fashion with a soft brush<br>3. Flossing as tolerated<br>4. Frequent rinsing with bland solutions, such as normal saline with sodium bicarbonate (1 liter water with 1/2 teaspoon baking soda and 1/2 teaspoon salt), moisturizing agents<br>5. Periodic dental evaluations and cleanings<br>6. Lifelong daily dental fluoride prophylaxis<br>7. Alcohol-containing chlorhexidine mouth rinse not recommended[31] | Standard practice to prevent infections, and potentially help alleviate mucosal symptoms |

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| 5. Oral decontamination | 1. Nystatin rinse not effective[32]<br>2. Systemic fluconazole *vs* no treatment dramatically reduces both candidal carriage and incidence of severe mucositis[33]<br>3. Antimicrobial lozenges[34]<br>4. Acyclovir and its analogs[35,36] | Hypothesis<br>1. Microbial colonization of oral mucositis lesions exacerbates the severity of oral mucositis and therefore, decontamination may help to reduce mucositis<br>2. Multiple studies have demonstrated that maintenance of good oral hygiene can reduce the severity of oral mucositis<br>3. Patients receiving radiation therapy alone are less likely to develop severe local infection<br>4. Prophylactic use of any of the antimicrobials is not recommended<br>5. Drugs, such as fluconazole, acyclovir and valacyclovir have well-established infections |
| 6. Magic mouthwash | Viscous combination of antacids, diphenhydramine, topical antifungal nystatin with viscous lidocaine[31] | Although these are popular, there has been no formal testing of such combinations |
| 7. Managing copious mouth/throat secretions/dry mouth | 1. Salt and soda solution<br>2. Guaifenesin<br>3. Anticholinergics | 1. Help in the early phases of secretion management<br>2. Also liquefy early-phase secretions, but may not be helpful because secretions thicken in later phases<br>3. Later-phase or larger-volume mucus may respond to combination narcotics, and anticholinergic drying agents found in selected cough preparations |
| 8. Management of bleeding | Topical agents like fibrin glue, gelatin sponge | May help in stopping bleeding temporarily |
| 9. RT conformality | 3D CRT, IMRT planning | 1. May be used to limit the mucosal volumes exposed, "hotspots" and dose to functionally important structures<br>2. Peak rates of high-grade mucositis may not differ between 2-dimensional, 3-dimensional and IMRT<br>3. IMRT has the potential to limit the total volumes of mucosa involved with high-grade mucositis, thus reducing overall short- and long-term morbidity |
| 10. Therapeutic interventions | Amifostine | FDA approved to decrease the rates and severity of both acute and chronic xerostomia. The impact on mucositis when is not clearly known. Because salivary mucins protect the mucosal surface, and saliva is antimicrobial and contains mucosal growth factors, the salivary preservation afforded by amifostine may have an indirect effect on mucositis. There is no recommendation for/or against the use of amifostine for mucositis prevention during head and neck RT |
| | Cryotherapy | Mainly as ice chips for prevention of mucositis in short bolus chemotherapeutic infusions, and does not have a role in radiation-induced oral mucositis |

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| | Growth factors<br>G-CSF<br>GM-CSF (subcutaneous, topical)<br>Erythropoietin | All have failed to show any benefit, and are not recommended for use during RT |
| | Palifermin | The phase II study, weekly 10 doses showed reduced mucositis, dysphagia and xerostomia during hyperfractionated radiotherapy but not during standard radiation therapy or chemoradiation group[37] |
| | | It was hypothesized that a lack of consistent activity in this trial was because of the use of a suboptimal dose schedule (weekly 60 gm/kg) |
| | | This led to dose finding studies confirming 60 gm/kg as a single dose, suboptimal in inducing epithelial cell proliferation as measured by Ki-67 staining but achieved with higher doses. Phase III industry-sponsored trials evaluating palifermin at these higher dose is awaited |
| | Anti-inflammatory agents—<br>Benzydamine hydrochloride[38] | A NSAID that inhibits proinflammatory cytokines including TNF-$\alpha$. In phase III trial, reduced the severity of mucositis in radiation therapy of cumulative doses up to 50 Gy |
| | | Based on this and previous studies, the MASCC/ISOO guidelines recommended use of this agent in patients receiving moderate-dose radiation therapy |
| | | But a recent phase III trial in radiation-induced oral mucositis was halted based on negative results of an interim analysis |
| | | Oral suspension of L-glutamine may reduce mucosal injury by reducing the production of proinflammatory cytokines and cytokine-related apoptosis and may promote healing by increasing fibroblast and collagen synthesis |
| | Saforis (topical agent) | In phase III study, reduced the incidence of clinically significant chemotherapy-induced oral mucositis as compared to placebo |
| | | RK-0202 combination of the thiol antioxidant N-acetyl cysteine and a proprietary vehicle for transmucosal delivery[39] |
| | N-acetyl cysteine (antioxidant) | A randomized phase II showed reduced oral mucositis incidence as compared with placebo control, justifying a phase III trial to confirm efficacy |
| | | LLLT or “soft laser” is thought to have analgesic, anti-inflammatory and wound healing effects and no known clinical toxicity |
| | | The optimal details of the technology including the type of light source, wavelength and dose schedule are not yet worked out, and its use requires training and certification. |
| | Low-level laser therapy | MASCC guidelines suggest LLLT use in the transplant setting but do not offer any specific recommendation during RT for HNC for which there are less available data[40,41] |
| | Targeting inflammation<br>Steroidal and nonsteroidal anti-inflammatory agents (betamethasone, prednisolone)<br>Prostaglandins E1 (misoprostol) and E2 (prostin) | did not reduce mucositis in clinical trials. |

## Future Directions in Mucositis Research

It is quite reasonable to see future as exciting for new research activities in search of agents active in management of mucositis. Many new drugs are under trial. Future studies should evaluate if agents that work by different mechanisms can be used in combination for greater clinical effectiveness. Another approach that would be looked for, is the use of novel drug delivery technologies that increase uptake of the active agent (e.g. glutamine) to the oral epithelial cells. Also, developing improved algorithms to predict the risk for the development of clinically significant mucositis would be valuable, so that patients at increased risk can be targeted for therapy in a more cost-effective manner.

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