

## Oral Mucositis - A Hindrance in Management of Oral Malignancy

Research Article

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### Abstract

Oral Mucositis (OM) is one of the major and the commonest toxicities of cancer therapy. It occurs in almost all patients who undergoes radiation therapy or chemotherapy in which the mucosal areas of oral and oropharyngeal region are included in the treatment zone. The pathophysiology of oral mucositis has always been a puzzle to the physicians and there are still many unanswered questions left about the risk factors for developing OM. Clinicians and researchers should join hands in pursuit of understanding and expanding the treatment strategies for Management of inflammatory conditions like OM in oncology. This will lead path to development of effective treatments and thereby reducing the burden of Oral mucositis and other inflammatory conditions in oncology. This article summarizes and gives clear insight on the risk factor, patient factors that is responsible for developing OM, elaborates the pathogenesis, clinical presentation, grading and management of the condition in detail.

**Keywords:** Oral Mucositis, Radiotherapy, Chemotherapy, HSCT.

### Introduction

Oral mucositis is a severely debilitating condition that occurs during the Treatment of malignancy with radiation therapy (RT), chemotherapeutic agents, and hematopoietic stem cell transplantation (HSCT)[1]. It represents an area of erythema followed by rupture of the oral mucosa with subsequent pain and reduction in oral intake. The lesions can also shatter the skin barrier resulting in local or systemic infection.[2] In severe cases, this can lead to nutritional deficiency and ultimately lead to poor quality of life. [3] This article gives an insight into the diagnosis and management of oral mucositis and the role of the interdisciplinary team in managing complications of oral mucositis to improve patient wellbeing.[4]

### Epidemiology

The incidence of Oral Mucositis depends upon the intensity of the drug and radiation and duration of the treatment.[8] A study reported that patients who receive high doses of chemotherapy

or undergo bone marrow transplantation have a 76 % risk of getting mucositis. Radiation-induced oral mucositis (RIOM) occurs in 100% of altered fractionation radiotherapy head and neck cancer patients.[7] Patients with poor nutritional status and poor oral care are more susceptible to developing Oral mucositis. [6]

### Pathophysiology [8]

The pathophysiology behind the development of oral mucositis due to chemotherapy and radiotherapy is thought to be due to a complex process that starts with injury to the tissue. This mechanism is described in a five-phase model suggested by Sonis.

**Phase 1: Initiation of tissue injury:** Radiation and/or chemotherapy induce direct cellular damage resulting in lysis of the basal epithelial cells. The generation of reactive oxygen species (free radicals) by radiation or chemotherapy is also believed to exert a role in the initiation of mucosal injury. These small highly reactive molecules are by-products of oxygen metabolism and can cause significant cellular damage.

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**Phase 2: Messaging and Signalling:** Besides causing direct cell death and production of free radicals it also upregulates inflammation via the production of messenger signals. The free radicals produced in the previous phase activate the second messengers that transmit signals from the cell surface receptors to the internal environment of the cell. This leads to the upregulation of pro-inflammatory cytokines which in turn leads to tissue injury and cell death.

**Phase 3: Signaling and amplification:** increased production of proinflammatory cytokines like tumor necrosis factor-alpha (TNF- $\alpha$ ), not only leads to mucosal cell injuries besides activates molecular pathways that in turn amplify mucosal injury.

**Phase 4: Ulceration and inflammation:** Due to the upregulation of proinflammatory cytokines the mucosa is infiltrated with an enormous number of inflammatory cells associated with the mucosal ulcerations, furthermore the metabolic by-products (pro-inflammatory cytokines) of the colonizing oral microflora also further upregulates the process and leads to secondary infection.

**Phase 5: Healing:** Healing is characterized by epithelial proliferation and cellular differentiation which contributes to restoring the integrity of the epithelium.

### Clinical Presentation

Mucositis is usually limited to non-keratinized surfaces of the Oral cavity e.g. buccal and labial mucosa, lateral tongue, ventral tongue, and soft palate.[4] Patients complain of discomfort/pain with eating or may have increased bleeding while brushing. Oral mucositis due to RT begins after the initiation of treatment to the head and neck it starts as acute inflammation in the oral mucous membrane like buccal mucosa, tongue, and pharynx and lasts between 7 and 98 days.[10] furthermore, oral mucositis due to chemotherapy has a periodic association with the dose of cytotoxic drug usually develops within 1 - 2 weeks of the given quantity [11]. It initially develops as erythema which later progresses into erosion and ultimately ulcerates later the ulcerated region is covered with a pseudomembranous layer which eventually peels off. [12] In patients undergoing HSCT, the oral mucositis resolves as the absolute neutrophil count recover.

### Evaluation

History and Clinical examination play a key role in the evaluation of Oral Mucositis. The intensity of oral mucositis is evaluated on a well-defined scale. Various scales like.

Common Terminology Criteria for Adverse Events (CTCAE), Oral Mucositis Assessment Scale (OMAS), Eastern Cooperative Oncology Group, and WHO scale. Out of all the available scales,

the Universally accepted is the WHO scale which combines both subjective and objective measures of oral mucositis.[13,14].

## Management

### Oral Hygiene Protocol

Maintenance of good oral hygiene protocols has been shown to help prevent mucositis and shorten the duration and intensity. Furthermore, It also helps to cut down the microbial load in the oral cavity which prevents the development of secondary infections.[16] Regular Oral care includes removal of dentures, gentle cleansing which includes flossing and brushing using ultra-soft bristles, and oral rinses. Several Oral rinses are available which include saline water rinse, sodium bicarbonate rinse, a mix of sodium bicarbonate and saline water, hydrogen peroxide (diluted 1:1 with saline or water), and miracle mouthwash.[1]“Magic mouthwash” which consists of diphenhydramine, viscous lidocaine, bismuth subsalicylate, and corticosteroid has proven to be the best mouth wash for treating oral mucositis [17].

### Pain Management

Topical anesthetic agents such as lidocaine are efficacious in reducing the intensity of the lesions and also relieves pain; however, this effect varies depending on the agent used. Topical agents would be a great at-home treatment option to allow for relief of pain and reduction in inflammation Also, opioid analgesics are given to alleviate pain.[16]

### Chemoprotective Agent

Palifermin is a keratinocyte growth factor and works as a chemoprotective agent, which has been recommended for severe oral mucositis (mucositis greater than or equal to grade 3) associated with autologous hematopoietic stem cell transplant regimens. In such patients, it has been shown to decrease the incidence and duration of severe oral mucositis. [16]

### Low-Level Laser Therapy

low-level laser therapy is being currently explored to amplify wound healing with a reduction in pain and inflammation; Nevertheless, standard treatment protocols are not currently present for all chemotherapy agents. A double-blinded study showed that low-level laser therapy was beneficial in the prevention of oral mucositis in patients receiving high-dose chemotherapy for HSCT.[17] It has been postulated that low-level laser therapy combats against the production of reactive oxygen species and/or pro-inflammatory cytokines that imparts a role in the pathogenesis of mucositis.

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

## Cryotherapy

For some chemotherapy agents, data suggests the use of placing ice chips in the mouth is beneficial, for example, during bolus of 5-fluorouracil and high dose melphalan.[18]

## Antioxidants

Amifostine which is a radioprotective agent is believed to act as a scavenger of reactive oxygen species which are potential agents to initiate mucositis. However, due to insufficient data, a MASCC/ISOO guideline could not be established regarding the usage of this agent in oral mucositis in patients receiving chemotherapy or radiotherapy. The topical application of amifostine in the oral cavity consists of the antioxidant, N-acetylcysteine. In a placebo-controlled trial in patients receiving radio and chemotherapy with head and neck cancer, amifostine remarkably reduced the incidence of severe oral mucositis up to doses of 50 Gy radiation.[19]

## Anti-inflammatory Agents

Benzydamine hydrochloride is a non-steroidal anti-inflammatory drug that suppresses the pro-inflammatory cytokines including TNF- $\alpha$ . In a Phase III trial, benzydamine hydrochloride mouth rinse reduced the intensity of mucositis in patients with head and neck cancer undergoing radiation therapy up to a total dose of 50 Gy radiation therapy. [20] Based on this report and other literature, the MASCC/ISOO guidelines recommended the use of Benzydamine hydrochloride in patients receiving moderate-dose of radiation therapy. Nevertheless, this agent has not received approval for this use from the U.S. FDA; besides, most patients with head and neck cancer receive over 50 Gy radiation therapy along with concomitant chemotherapy. A more recent Phase III trial of Benzydamine hydrochloride in radiation-induced oral mucositis in patients with head and neck cancer was discontinued based on negative results of an interim analysis.

## Zinc Supplementation

Zinc helps in the re-epithelisation of the tissues as well as scavenges the free radicals and protects the mucosa from further damage. It is beneficial as adjuvant therapy in patients with oral cancer undergoing chemoradiation.[16]

## Diet

Diet during the period of mucositis plays a pivotal role in managing the flare-up of the condition. The diet is restricted to soft and bland food that doesn't traumatize the oral mucosa. Foods that contain less salt, and acid are advisable, sipping water frequently helps to combat the friction of the oral mucosa due to lack of saliva which in turn prevents further damage.[11]

## Conclusion

Radiotherapy and Chemotherapy can be associated with multiple side effects among which oral mucositis is the condition which produces major discomfort to the patient. It also hinders patient's quality of life. As it becomes well understood, most of these side effects cannot be avoided. Several preventive measures are taken

in order to limit their expression. The oral cavity is a usual site of discomfort and pain caused by Mucositis. The role of dentist is pivotal in managing oral mucositis to provide relief to the suffering patients.

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