REVIEW ARTICLE

Strategies in Management of Oral Mucositis

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Abstract

Oral mucositis is a clinically important and sometimes dose-limiting complication of Cancer Therapy. Mucositis lesions are painful, affect nutrition, quality of life and often hampers continuity of the treatment modality. The pathogenesis of oral mucositis is multifactorial and complex. This is a review paper which discusses various aspects a clinician should know in management of mucositis.

Keywords: Mucositis, cancer, chemotherapy tumor necrosis factor (TNF).

INTRODUCTION

Oral mucositis is a common and debilitating painful side-effect of many forms of chemotherapy and radiation therapy. The erythematous, atrophic and ulcerative lesions that develop are a consequence of epithelial damage and death mediated through a complex series of molecular and cellular events.

The consequences of mucositis is detrimental so much that it may result in chemotherapy dose reductions, breaks in radiation, administration of narcotics, hospitalization and morbidity.

Although, the clinical impact of oral mucositis might be under-appreciated by most health care professionals, the same is certainly not held by individuals who report mucositis.

CLINICAL SIGNIFICANCE OF ORAL MUCOSITIS

The severity of oral mucositis varies from mild erythema, with mucosal discomfort and burning sensation to large, deep eroded, coalescing ulcers which render high doses of opoids for intervention. The oral cavity proves to be a good medium for the flourishing of all-bacteria, virus and fungi. Hence, mucositis is a known factor for bacteremia and sepsis.

Patients undergoing chemotherapy and radiation therapy for cancers of head and neck, show mucosal changes after a cumulative radiation dose. Ulcerative lesion begin to show-up by the end of third week, when almost 30 Gy of radiation dose is taken.

Chemotherapy-induced mucositis typically begins 4 to 5 days following the infusion and peaks 5 days later. The lesions are usually limited to nonkeratinised surfaces-like lateral and ventral surface of tongue, buccal mucosa and soft palate. Selected agents such as antimetabolites and alkylating agents cause a higher incidence and severity of oral mucositis. Effects of oral mucositis is so severe that patients opt to take breaks from their therapies leading to break in the regime planned by the oncologist. And due to inappropriate management, consequently there is sub-optimal cancer treatment.

ETIOPATHOGENESIS OF ORAL MUCOSITIS

Studies show that the fundamental mechanisms involved in pathogenesis of mucositis are much more complex than direct damage to epithelium alone.[1] Mechanisms for radiation-induced and chemotherapy-induced mucositis are believed to be similar.

Following is the five-staged model for the pathogenesis of mucositis.[2]

Diagram 1 showing five stage model of oral mucositis. Therefore to sum up:

1. *Initiation of tissue injury*: Radiation and/or chemo-therapy induce cellular damage resulting in death of the

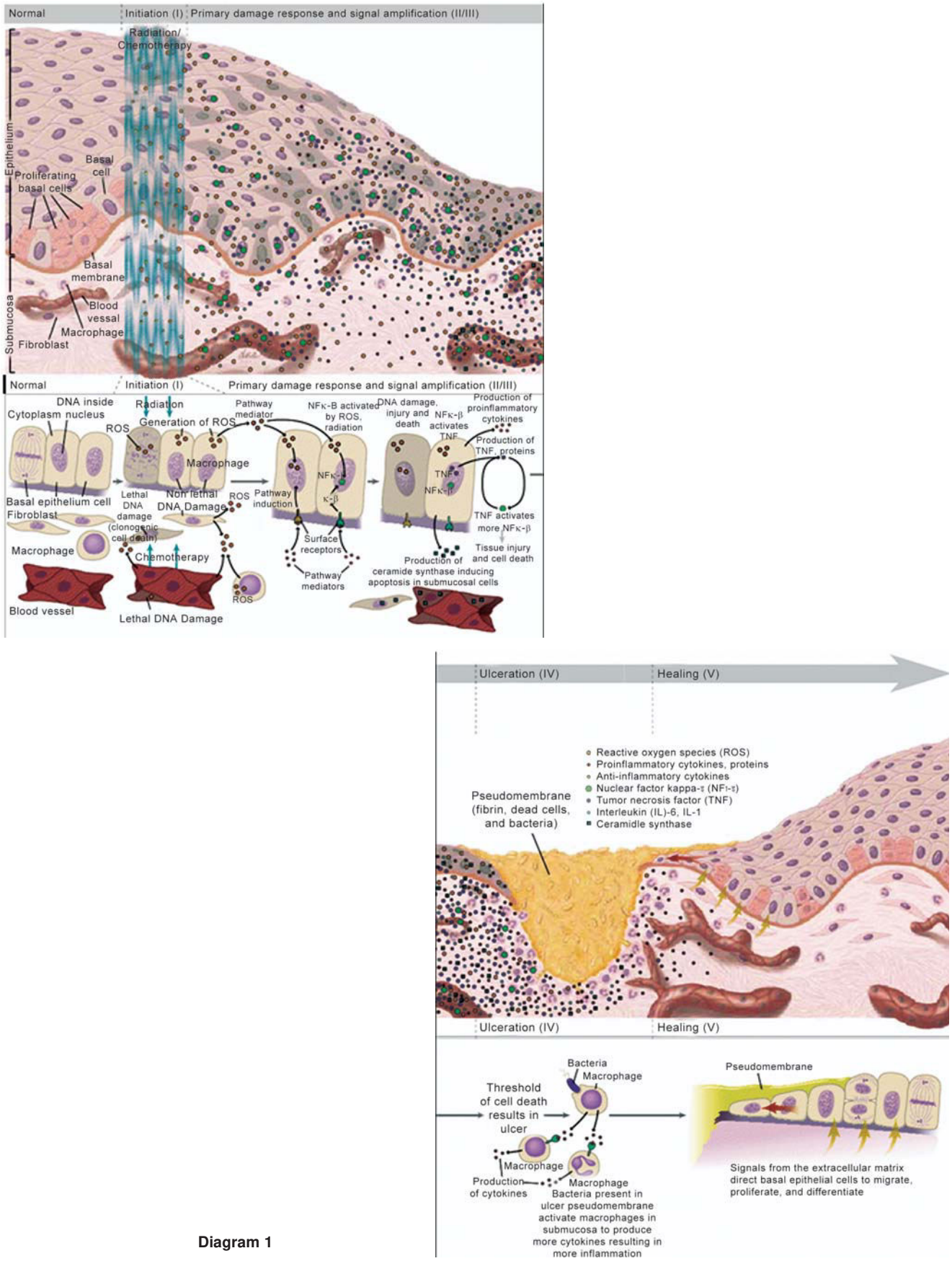
Normal
Initiation (I)
Primary damage response and signal amplification (II/III)
Radiation/ Chemotherapy
Epithelium
Basal cell
Proliferating basal cells
Basal membrane
Blood vessal
Macrophage
Fibroblast
Submucosa
Normal
Initiation (I)
Primary damage response and signal amplification (II/III)
DNA inside Cytoplasm nucleus
Radiation
Generation of ROS
ROS
Pathway mediator
NFκ-B activated by ROS, radiation
DNA damage, injury and death
NFκ-β activates TNF
Production of proinflammatory cytokines
Production of TNF, proteins
Macrophage
Basal epithelium cell
Fibroblast
Lethal DNA damage (clonogenic cell death)
Non lethal DNA Damage
ROS
Pathway induction
NFκ-β
TNF
TNF activates more NFκ-β
Tissue injury and cell death
Surface receptors
Pathway mediators
Production of ceramide synthase inducing apoptosis in submucosal cells
Macrophage
Chemotherapy
Blood vessel
Lethal DNA Damage
ROS
Ulceration (IV)
Healing (V)
Reactive oxygen species (ROS)
Proinflammatory cytokines, proteins
Anti-inflammatory cytokines
Nuclear factor kappa-ε (NFι-ε)
Tumor necrosis factor (TNF)
Interleukin (IL)-6, IL-1
Ceramidle synthase
Pseudomembrane (fibrin, dead cells, and bacteria)
Ulceration (IV)
Healing (V)
Bacteria
Macrophage
Threshold of cell death results in ulcer
Pseudomembrane
Macrophage
Production of cytokines
Macrophage
Bacteria present in ulcer pseudomembrane activate macrophages in submucosa to produce more cytokines resulting in more inflammation
Signals from the extracellular matrix direct basal epithelial cells to migrate, proliferate, and differentiate

Diagram 1

Table 1: Five stage model of oral mucositis (Courtesy journal of supportive dentistry; Volume 5, No. 9, Supplement 4, October 2007)

Initiation	*Upregulation and message generation*	*Signaling and amplification*	*Ulceration*	*Healing*
X-rays or chemotherapy cause direct DNA damage	The ceramide pathway signals cells to enter apoptosis	NFκ-β activated COX-2 produces prostaglandins	Submucosal cell death removes epithelial trophic factors such as KGF	COX-2 activation promotes new angiogenesis
X-rays or chemotherapy generate ROS	Damaged cell membranes stimulate sphingomyelinases	TNF-α activates NFκ-β and c-JUN	MMPs degrade the ECM	RM 2/3 macrophages downregulate inflammatory responses
ROS damage lipids, DNA, connective tissue, and other biomolecules	NFκ-β modulates the proinflammatory cytokines	Feedback loops reinitiate the damage response pathways	The ECMs wells with fluid weakening the attachment between submucosa and epithelium	Epithelial cells multiply and migrate to close the ulcerative wound
Chemotherapy stimulates ceramide synthase	NRF2 transcription factor activates antioxidant related genes	Damage responses are amplified in space and intensity	Clonogenic cell death reduced epithelial regeneration, and apoptosis thin the epithelium	Submucosal cells regenerate
X-rays stimulate nuclear factor kappa-β (NFκ-β)	NFκ-β modulates apoptosis genes in the BCL family	TNF-α stimulates apoptosis	Opportunistic infections release bacterial cell wall components, which stimulate inflammatory responses	Healing produces a new tissue that is not exactly the same as the old tissue

Abbreviation: NFκ-β = nuclear factor kappa-β; COX-2 = cyclooxygenase-2; KGF = keratinocyte growth factor; ROS = reactive oxygen species; TNF-α = tumor necrosis factor-alpha; MMPs = matrix metalioproteinases; ECM = extracellular matrix; NRF2 = nuclear factor erythroid-2 related factor 2

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.

2. Up-regulation of inflammation via generation of messenger signals.
   In addition to causing direct cell death, free radicals activate second messengers that transmit signals from receptors on the cellular surface to the inside of the cell. This leads to up-regulation of proinflammatory cytokines, tissue injury and cell death.
3. *Signaling and amplification*: Up-regulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), produced mainly by macrophages, causes injury to mucosal cells and also activates molecular pathways that amplify mucosal injury.
4. *Ulceration and inflammation*: There is a significant inflammatory cell infiltrate associated with the mucosal ulcerations based in part on metabolic by-products of the colonizing oral microflora. Production of proinflammatory cytokines is also further up-regulated as a result of this secondary infection.
5. *Healing*: This phase is characterized by epithelial proliferation as well as cellular and tissue differentiation, restoring the integrity of the epithelium.

Calibration of Oral Mucositis

Many scales have been reported to describe the extent and severity of oral mucositis.

*The World Health Organization (WHO) is easy and suitable for routine daily practice. It is as follows:

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

*The national cancer institute (NCI) common terminology criteria for adverse events (CTCAE) version 3.0 includes

two separate scales, objective and subjective scales for mucositis[3]:

***Oral Mucositis (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; life-threatening consequences
Grade 5	Death

***Oral Mucositis (Functional/Symptomatic)**

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

*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.

Table 2: Management of oral mucositis is divided into sections

Sr. No.	Ailment	Notes	Treatment
1	Pain control	Pain significantly affects nutritional intake, mouth care and quality of life. The MASCC/ISOO guidelines recommend patient-controlled analgesia with morphine for patients undergoing hematopoietic cell transplantation[7]	• Saline mouth rinses, ice chips and topical mouth rinses containing 2% viscous lignocaine is often used in most centers. • Lidocaine + diphenhydramine + soothing or Kaopectate all in equal volumes can be mixed and administered locally. They provide short-term relief. • Sucrafate, a topical mucosal bioadherent which is not an anesthetic is postulated to reduce pain due to its quality of forming a protective covering over an ulcerated mucosa
2	Nutritional support	Nutritional intake can be severely compromised by the pain associated with severe oral mucositis. A soft diet and liquid diet supplements are more easily tolerated than a normal diet when oral mucositis is present.	In patients expected to develop severe mucositis, a gastrostomy tube is placed prophylactically, although this varies considerably from center to center. In patients undergoing hematopoietic cell transplantation, total parenteral nutrition is usually given via an indwelling catheter such as Hickman line.
3	Oral decontamination	It has been hypothesized that microbial colonization of oral mucositis lesions exacerbates the severity of oral mucositis and hence decontamination helps reduce mucositis.Multiple studies have demonstrated that maintenance of good oral hygiene can reduce severity of oral mucositis.[8-10] Patients who have undergone Hematopoietic cell transplantation and develop oral mucositis also have been found to be three times more likely to develop bacteremias resulting in increased length of hospital stays as compared to patients without mucositis.[11] So, oral decontamination may reduce mucositis that inturn my reduce bacteremia Oral decontamination can reduce infection of the oral cavity by opportunistic pathogens.[12] Hence oral decontamination is to reduce the systemic sepsis from resident oral and/or opportunistic pathogens. This is especially true in patients who are immunosuppressed as a result of chemotherapy	Patients and his caretakers need an emphasis on effective oral hygiene. MASCC/ISOO guidelines recommend use of a standardized oral care protocol including brushing with a soft tooth-brush, flossing and use of non-medicated rises; e.g. saline, sodium bicarbonate rinses. Alcohol containing chlorhexidine mouth rinses may be difficult for patients to tolerate, hence not administered.[7] Nystatin rinses is not found to be much effective.[13] Systemic Fluconazole has shown significant and dramatic reduction in candidiasis and mucositis induced due to radiation therapy for HFN cancers. MASCC/ISOO guidelines recommend against the routine use of antimicrobial lozenges of acyclovir and its analogs to prevent mucositis.

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Sr. No.	Ailment	Notes		Treatment
4	Palliation of dry mouth	Patients undergoing cancer therapy often develop transient or permanent xerostomia and hyposalivation. Hyposalivation can further-aggravate inflamed tissues-increase risk for local infection-poor masticatory efficiency Many patients complain of thickening of saliva which is due to decrease in serous component of saliva		Following measures to be taken: – Regular sips of water to alleviate mouth dryness – Administration of artificial saliva – Rinse mouth with a solution of half teaspoon baking soda in one cup of warm water. The swishing of this solution lubricates the tissues and buffers the oral environment. – Chew sugarless gum to stimulate salivary flow – Cholinergic drugs if necessary
5	Management of oral bleeding	Bleeding may occur from the ulcerations of oral mucositis		Local intraoral bleeding can usually be controlled with the use of topical hemostatic agents such as fibrin glue or gelatin sponge.[14] Patients whose platelet count falls below 20,000/ml may receive platelet transfusion because of the risk for spontaneous internal bleeding, which may have effects on CNS
6	Therapeutic intervention for oral mucositis	Cryotherapy	It has been hypothesized that topical administration of ice chips to oral cavity during administration of chemotherapy results in decreased delivery of chemotherapeutic agent to the oral mucosa.This effect is presumably mediated through local vasoconstriction and reduced blood flow	Studies have revealed that cryotherapy reduces the severity of oral mucosotis in patients receiving bolus doses of chemotherapeutic agents. Ice-chips are placed in the oral cavity, five minutes prior to chemotherapy and replenished as needed for up to 30 minutes. Cryotherapy is useful for short bolus chemotherapy.
		Growth factors	Reduction in the proliferative capacity of oral epithelial cells is thought to play a role in the pathogenesis of mucositis. Hence various growth factors that can increase epithelial cell proliferation. Furhter studies are ongoing to confirm the safety of epithelial growth factors in solid tumor setting including patients receiving radiation therapy for HFN cancers	Evidences show that intravenous infusion of human keratinocyte growth factor -1 [paliferamin], significantly reduces incidence of WHO grade 3 and 4 oral mucositis.[15] Human keratinocyte 2-{Repifermin}, related compound have has shown to be ineffective in this direction[16] Intravenous human fibroblast growth factor-20 [Velafermin] is currently in clinical development for reduction of mucositis secondary to high-dose chemotherapy[17]
		Anti-inflammatory agents	Benzydamine hydrochloride is a nonsteroidal anti-inflammatory drug that inhibits proinflammatory cytokines including TNF-α. L-glutamine enhances the uptake of amino acid into epithelial cells. Glutamine may reduce mucosal injury by reducing the producing the production of proinflammatory cytokines and cytokine-related apoptosis and may promote healing by increasing fibroblast and collagen synthesis	MASCC/ISOO guidelines recommended use of this agent in patients receiving moderate-dose radiation therapy.[18] However this agent has not received approval from FDA. A study showed that oral suspension of L-glutamine reduced the incidence of clinically significant chemotherapy-induced oral mucositis. MASCC/ISOO guidelines recommend that systemically administered glutamine not be used for GI mucositis because of lack of efficacy.[19]

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Sr. No.	Ailment	Notes		Treatment
		Antioxidants	Amifostine is thought to act as a scavenger for harmful reactive oxygen species that are known to potentiate mucositis.[20] N-Acetylcysteine in a proprietary matrix for topical application in the oral cavity	
		Low-level laser therapy	It has been speculated that low-level laser therapy may reduce levels of reactive oxygen species and/or proinflammatory cytokines that contribute to the pathogenesis of mucositis	MASCC/ISOO suggest use for centers which can support the necessary training and technology[21]

This scale has been validated in a multicenter trial with high inter-observer reproducibility and strong correlation of objective mucositis scores with patient symptoms.[4]

The eastern co-operative oncology group (ECOG) common toxicity criteria are also used in oncology trials to document severity of oral mucositis.[5]

Management of Oral Mucositis

Based on a comprehensive systematic review of literature, the mucositis study group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) has developed clinical practice guidelines for management of mucositis[6] (Table 2).

SUMMARY

Oral mucositis has emerged as a clinically important complication of selected cancer therapies. The incidence of oral mucositis can be close to 100% in patients receiving certain conditioning regimens in inticipation of hemato-poietic stem-cell transplant or radiation therapy, with/without chemotherapy for cancers of head, face, neck (HFN). Two-thirds of patients being treated for cancers of the larynx or hypopharynx suffer from mucositis. It is almost ubiquitous in patients receiving induction therapy for leukemia and oral mucositis affects between 25 to 33%[22,23] of patients who receive multicycle chemotherapy for the treatment of most common solid tumors.

Although, the condition has been evident for several decades, it is only lately new model for pathogenesis has been defined. This model has facilitated designing of effective foundation for improvising target therapies at the cellular levels. Hence newer drugs can be formulated, developed and prescribed over a period of time. This in turn would aid the health care personnel to customize therapy according to the risk for developing the condition.

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