Radiotherapy and Chemotherapy induced Oral Mucositis – Prevention and Current Therapeutic Modalities

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INTRODUCTION
Oral mucositis is a distressing toxic effect of radiotherapy and systemic chemotherapy in cancer patients.¹ Mucositis is characterized by atrophy of squamous epithelial tissue, vascular damage, and an inflammatory infiltrate concentrated at the basement membrane and is followed by ulceration.² Oral mucositis is associated with significant morbidity characterized by pain, odynodysphagia, dysgeusia, malnutrition, dehydration and it also increases the risk for systemic infections in immunocompromised patients.³

Oral mucositis can occur with cumulative radiotherapy doses as low as 1000-2000 cGy with therapy administered at a rate of 200 cGy per day.⁴ In greater than half of patients with mucositis, the condition is of such severities so as to require parenteral analgesia, interruption of Radiotherapy, and hospitalization, all of which increase the cost of cancer therapy and have a negative impact on quality of life.⁵

PATHOPHYSIOLOGY
While our understanding of the molecular and cellular pathways leading to mucositis is still evolving, it is now clear that the condition represents the culmination of a dynamic sequence of events that involve all cells and tissues in the mucosa. Five phases characterize the pathophysiologic progression that results in mucositis: initiation, up regulation and signaling, amplification, ulceration, and healing. Each phase offers a potential target for therapeutic intervention. ⁶

Phase 1 (Initiation): radiation or chemotherapy causes DNA damage in basal epithelial cells and generates reactive oxygen species (ROS), which further damage cells and blood vessels in the submucosa.

Phase 2 (Signaling): Radiation, chemotherapy, and ROS induce apoptosis and up regulate inflammatory cytokines in cells.

Phase 3 (Amplification): inflammatory cytokines produce further tissue damage, amplifying signaling cascades and the injury process.
Phase 4 (Ulceration): loss of mucosal integrity produces extremely painful lesions, providing portals of entry for bacteria, viruses, and fungi.

Phase 5 (Healing): proliferation, differentiation, and migration of epithelial cells to restore the integrity of the mucosa.6, 7

TREATMENT MODALITIES

An intensive oral hygiene protocol involving treatment of carious teeth and maintaining proper oral hygiene reduce the activity of oral microflora to prevent or reduce the discomfort associated with oral mucositis. Apart from these, treatment options for mucositis can be broadly categorized into:

LOCALLY APPLIED NON-PHARMACOLOGICAL METHODS

Cryotherapy probably causes local vasoconstriction and thus temporarily reduces blood flow during the time of peak serum drug concentrations and also decreases the drug delivery to oral mucosal cells. Patient swishes ice chips in the mouth for a total of 30 mins, starting 5 mins prior to each dose of drug.3, 8

Lasers like helium–neon lasers and other soft lasers have been reported to produce analgesia and wound healing. Studies of laser effects in human have generally documented to decrease pain, inflammation, and oedema in laser treated tissues.1, 3, 8

Radiation shields are constructed to protect uninvolved oral tissues during radiation. Preliminary data suggest that removal of detachable parts of prosthesis, fabrication of protective stents and midline mucosa sparing blocks are used to reduce irradiation of uninvolved mucosa and to avoid scattered radiation from implants and dental restoration. This may reduce the oral complication of radiotherapy without affecting the tumor.1, 3, 9

TOPICALLY APPLIED PHARMACOLOGICAL METHODS

A variety of mouthwashes with mixed actions have been evaluated in treatment of oral mucositis induced by radiotherapy and chemotherapy.

Benzydamine hydrochloride is a drug which has anti-inflammatory, anesthetic, analgesic, anti-pyretic and antimicrobial activities, and has been used as a mouthwash to prevent and treat oral mucositis.10

There is good evidence that Benzydamine hydrochloride mouthwash is effective in improving the symptoms of radiation-induced mucositis in patients with head and neck cancer.4, 10-14

Chlorhexidine a bisguanidine exhibiting broad spectrum anti-bacterial and antymycotic activity is perhaps one of the most commonly used mouthwash.10 However randomized trial failed to confirm the postulated effects and hence cannot be recommended for prophylaxis of both chemotherapy and radiotherapy induced mucositis.15, 16, 17

Povidone iodine has a wide antiseptic effects including antiviral, antibacterial and antifungal efficacy and its good tolerability have resulted in frequent use as preventive and therapeutic drug in radiotherapy and chemotherapy induced mucositis.18, 19

Chamomile a solution prepared from a flower of Chamomile plant contains chamazulene, levemnol, polyins and flaviniods. The combination of these constituents have anti-inflammatory, spasmylocytic effects, promote granulation and mucosal healing. Mouthwashes applied prophylactically delayed the onset and reduced the severity of radiation mucositis and prevented the occurrence of severe mucositis.1, 10, 20

Glucorticorticoids are anti-inflammatory drugs inhibiting synthesis of inflammatory proteins with involvement of complex mechanism at molecular level, which leads to decrease in transcription of genes involved in inflammation. Use of high dose of methasone mouthwash before and during radiotherapy showed progressive whitening as radiation progressed, which was in contrast to erythema that usually occurs. The mucosa remained virtually ulcer free with no discomfort or bleeding of mucosa.1

Sucralfate is a basic aluminium salt of sucrose sulfate and when contacted with ulcerated mucosa, sucralfate generates a paste like protective coat by forming ionic bonds to proteins. In addition sucralfate promotes the local production of prostaglandins, which acts as a cytoprotectant stimulating epithelial proliferation, migration, blood flow and mucus production.1, 3, 10, 21

Prostaglandin E2 is a derivative of misoprostol, which is considered to have anti-inflammatory properties, has produced controversial results. A prophylactic study enrolling patients undergoing radiotherapy found an impressive reduction of severe cases of radiotherapy induced mucositis and in contrast patients undergoing chemotherapy did not benefit from use of prostaglandins. These findings are
mirrored by randomized placebo-controlled trial demonstrating that systemic administration of indomethacin, a cyclo-oxygenase inhibitor, significantly reduced the severity and delayed the onset of radiotherapy induced mucositis.\textsuperscript{1, 3, 10, 2, 22}

**Retinoids** is known to stimulate wound healing and has been found to reduce oral complications by exerting inhibitory effects upon inflammation, induces epithelial growth and enhances mucosal resistance to cycle-specific toxicities. Supplemental **dietary beta-carotene** has shown to decrease the severity of chemotherapy and radiotherapy induced mucositis.\textsuperscript{1, 3, 23}

**Vitamin E**, the rationale for topical use is based on its antioxidant and membrane stabilizing potency, thus interfering with the inflammatory damage caused by reactive oxygen species and free radical created in the course of radiotherapy and chemotherapy. Tocopherol is inexpensive, readily available, well tolerated and clinical trials have shown significant improvement in reducing severity of mucositis.\textsuperscript{1, 3}

**Glutamine**, which is a major energy source for mucosal epithelial cells and stimulates mucosal growth and repair, has been evaluated and the limited available evidence suggests that it may decrease the duration of mucositis, although further research is required.\textsuperscript{3, 10, 24}

**Antibiotic lozenges** designed to dissolve in the mouth and decontaminate the oral mucosa have been developed and have been widely recommended to reduce oral infections associated with mucositis. The lozenges contain **polymixin E (P)**, **tobramycin (T)** and **amphotericin B (A)**, which together provide broad spectrum antibacterial and antifungal cover. These are commonly known as PTA lozenges or PTA pastilles. There is some evidence supporting the use of PTA lozenges in preventing infectious complications of mucositis in cancer undergoing radiotherapy.\textsuperscript{3}

Mouth rinses containing **corticosteroids**, **disinfectants**, **antimicrobials**, **baking soda**, and **local anesthetics** are used in prophylaxis of chemotherapy or radiotherapy-induced mucositis. Mucositis cocktail (also know as “magic mouthwash”) containing corticosteroids have shown promising results in pilot studies conducted by Abdelaal et al.\textsuperscript{3, 10}

**Allopurinol and uridine** when used as mouth rinse reduces mucosal toxicities by inhibition of urotidylate decarboxylase, an enzyme responsible for intracellular formation of cytotoxic metabolites.\textsuperscript{1, 3}

**Dexpanthenol**, a granulation promoting agent, aluminium and milk of magnesia and kaolin–pectin are the part of many multiagent mouth rinses, although there efficacy has not yet been demonstrated.\textsuperscript{3}

**Capsaicin**, which is the active ingredient in chili and pepper and acts by desensitizing some neurons to provide temporary pain relief, has also been evaluated. Candies containing capsaicin have been promoted as an alternate analgesic treatment for chemotherapy-induced mucositis.\textsuperscript{1, 3, 10}

**Silver nitrate (2%)** solution when given few days before radiotherapy, reduced the severity of mucositis. It is suggested that silver nitrate can stimulate the unirradiated mucosa into a more effective proliferative state before the start of mucositis.\textsuperscript{3, 1}

**Mesalazine (5-amino-salicylic acid)** is an anti-inflammatory agent and have shown to inhibit the activation of one of the transcription factor involved in transcription of genes.\textsuperscript{25} Topical mesalazine is shown to be effective in treatment of aphthous ulcer and in **Behcet’s** disease.\textsuperscript{26} Preliminary studies of topical mesalazine have shown some benefits in treatment of chemotherapy and radiotherapy induced mucositis.\textsuperscript{27}

**Leucovorin (5-formyltetrahydrofolate)** is used to protect the normal tissues from the toxic effect of high dose methotrexate, a folic acid antagonist. Leucovorin mouthwash was expected to protect oral mucosal cell by antagonizing locally the inhibition of purine and thymidil at synthesis induced by methotrexate. However, in several studies, topical leucovorin did not effectively prevent the development of oral mucositis.\textsuperscript{1, 28}

**Hydrogen peroxide** applied as 1% rinsing solution failed to demonstrate as therapeutic drug in patients undergoing radiotherapy. Subsequent to rinsing with hydrogen peroxide, patients reported that symptoms of oral mucositis seemed to intensify, leading withdrawal of the drug due to glossdynia. Hence the use of hydrogen peroxide, for prevention or treatment of oral mucositis is discouraged.\textsuperscript{1, 10, 29}

**Multiple Activity (EN3247)**: Several new agents are in late-stage development, EN3247 (triclosan 0.1%) is an oral rinse possessing anti-inflammatory,
EN3247 targets the cyclooxygenase and lipoxygenase pathways, both of which have been demonstrated to have a role in carcinogenesis, immunosuppression, and inflammation. EN3247 has broad-spectrum antimicrobial activity. At bacteriostatic concentrations, it inhibits the uptake of essential amino acids and causes disorganization of the cytoplasmic membrane and cell leakage at bactericidal concentrations. Study data have demonstrated reductions in the occurrence and severity of mucositis. Patients who underwent high mucositis-producing treatment regimens and also received EN3247 experienced an average of 4.6 days of mucositis, compared to 6.12 days of mucositis among patients given a placebo.\textsuperscript{10}

Gelclair is a concentrated gel, and Zilactin is a protective film. When applied to the mucosa, both form a protective barrier. Not only do data indicate favorable oral pain control and relatively short onset times, but eating and speaking are facilitated because of the agents ability to adhere to areas that normally are traumatized by these activities.\textsuperscript{10}

Of all available mouth rinses that can be used as treatment for mucositis, the least costly and easiest for patients to prepare is a simple mouthwash comprising a teaspoon (10 ml) of salt and a teaspoon (10 ml) of baking soda in 8 ounces (250 ml) of water. A comparison among salt and soda mouthwashes, mouthwashes prepared from lidocaine and diphenhydramine with maalox, and mouthwashes of 0.12% chlorhexidine found that all the three options were equally effective in the treatment of chemotherapy induced mucositis.\textsuperscript{1}

**SYSTEMICALLY APPLIED PHARMACOLOGICAL METHODS**

Amifostine is a cytoprotective agent consisting of sulfhydryl compound, acts as antioxidant by scavenging free radicals generated in the tissue exposed to radiation and it also promotes repair of damaged DNA. There is reduced uptake of amifostine into tumor, and tumor protection is not seen. Administration requires prehydration, and intravenous administration prior to receiving radiochemotherapy. Mucosa protections have been reported when subcutaneous dosage of 500 mg and intravenous use at doses up to 740 mg/m\textsuperscript{2}. Side effects, mostly nausea, vomiting and hypotension seem to be pronounced at higher dose and IV use.\textsuperscript{1,3,10,30}

**Azelestine hydrochloride** is a potent histamine H\textsubscript{1} receptor and an antioxidant. It suppresses neutrophil burst and cytokine release from lymphocyte. Okasi et al reported a significant reduction of incidence and severity of oral mucositis during chemoradiation.\textsuperscript{1}

**Pentoxifylline** is a xanthine derivative, use of pentoxifylline can regulate endotoxin-induced production of TNF-alpha and possess profound immunomodulatory properties. Elevated levels of TNF-alpha have shown to correlate with development and severity of all transplant related complications. Oral pentoxifylline have shown to reduce the frequency and severity of all major complications including oral mucositis in clinical trial.\textsuperscript{1,31}

Anticholinergic drugs causes xerostomia by decreasing salivary flow, which may result in decreased mucosal secretion of certain cytotoxic drugs and reduce acute toxicities. Propantheline reduced significantly oral mucositis in patients treated with high dose of etoposide both as single agent and as multidrug regimen.\textsuperscript{1}

**Immunoglobulin** has shown to decrease the severity and duration of radiotherapy-induced oral mucositis when treated with low dose IM (Igm) immunoglobulin. It is probable that anti-inflammatory effects of exogenous immunoglobulin are responsible for the effects. Large infusions of immunoglobulin G have been shown to manipulate the immune system by regulating the function of T effector cells, inflammatory cytokine downregulation and complement modification.\textsuperscript{1,3,32}

Pineal hormone melatonin inhibits the production of free radical that mediates toxicity of chemotherapy. Experimental data have suggested that it counteracts chemotherapy induced mucositis.\textsuperscript{33}

**GROWTH FACTORS: A RECENT ADVANCE IN THE PREVENTION AND TREATMENT OF MUCOSITIS**

Growth factors that may have an impact on mucositis are granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), Interleukin 11 (IL-11), and keratinocyte growth factor (KGF). The first recombinant growth factors to be evaluated are G-CSF and GM-CSF. The most promising growth factor for the prevention of mucositis is KGF, which has demonstrated a reduction in incidence and severity of mucositis in several clinical trials.
CSF and GM-CSF; there are two theories on the mechanism of oral mucositis reduction by G-CSF and GM-CSF. First one supposes that neutropenia may predispose the patient to oral infections, which aggravate oral mucositis. G-CSF and GM-CSF may reduce oral mucositis by accelerating neutrophil recovery. The second, more likely mechanism may be a direct stimulative effects of G-CSF and GM-CSF on the growth or regeneration of oral mucosa thereby helping prevention and treatment of chemotherapy induced mucositis.1,10,34,35

GM-CSF mouthwashes have been shown to cause marked alleviation of existing oral mucositis in several studies without detectable systemic accumulation of GM-CSF upon systemic neutrophil count. Subcutaneous application of GM-CSF during radiotherapy has been shown to reduce oral toxicities when compared to other historic drugs. The systemic administration of GM-CSF was found to significantly reduce the incidence and severity of oral mucositis in patients undergoing chemotherapy. GM-CSF was also found to shorten the duration of mucositis in some myeloablative regimen. These results are probable due to lack of mucosal accumulation of GM-CSF subsequent to subcutaneous administration. Similarly, the prophylactic use of GM-CSF during radiotherapy reduced treatment interruption and the occurrence of severe mucositis without, altering the incidence or severity of oral mucositis.10, 34

Interleukin-11 a human recombinant is a pleiotropic cytokine. In animal models, it has been found to reduce gut and mucosal permeability, partially polarize T-cells to a Th2 phenotype, down-regulate IL-12, prevent mucositis, and accelerate recovery of oral and bowel mucosa.1, 3, 35

KGF (palifermin): Keratinocytes are cells that secrete proteins which are important components of epithelial cells. KGF is a naturally produced substance that stimulates the growth of keratinocytes. Palifermin is a substance developed through laboratory processes to protect keratinocytes from damage caused by chemotherapy and radiation and thus protect patients against mucositis. Results indicate that palifermin appears to both prevent and reduce oral mucositis in a significant portion of patients undergoing conventional 5-FU chemotherapy or high-dose chemoradiotherapy with stem cell transplantation. Palifermin reduced the incidence of grade 2-4 from 78% to 32% and decreased the duration of severe mucositis from 10.2 days to 3.4 days.30 Palifermin reduced the incidence of grade 3-4 mucositis from 98% to 63% and grade 4 mucositis from 62% to 20%. The reduction in mucositis was associated with less opioid use and less total parenteral nutrition in the palifermin group. Upon completion of clinical trials and subsequent approval by the FDA, palifermin will be the first drug available for the prevention of mucositis and shows promise for significantly improving quality of life and outcomes.10, 36, 37

CONCLUSION

Oral mucositis is a common and important side effect of many cancer therapies. No definitive approach to the prevention or treatment of oral mucositis has been identified yet. Continual assessment and monitoring of high-risk patients are necessary for the effective management of oral mucositis. The systematic use of evidence-based, goal-driven oral care regimens can help reduce the incidence and severity of oral sequelae. Novel therapies for the management of oral mucositis currently are in development, and, ultimately, effective management strategies may broaden to include systemic agents with multiple targets. Results with the administration of growth factors and radical scavengers are promising and need further study that focuses on prevention of mucositis.

REFERENCES:


