

# Management of oral mucositis

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## SUMMARY

*Oral mucositis is one of the most common oral complications of cancer treatment. Studies have shown some interventions that reduce the severity of this condition, but there is not a specific treatment proved that really prevents or treats mucositis efficiently. The aim of this paper was to provide a literature review for better understanding of the management of oral mucositis. Pubmed and Scopus were used in order to identify research articles published between 2005 and 2012 in English language. A search term combination that included stomatitis, mucositis, lasers, complimentary therapies, amino acids, antioxidants, vitamins, minerals, plant extracts, and cryotherapy was conducted. A large number of therapeutic strategies to prevent and treat oral mucositis have been shown in studies and growth factors, including palifermin, appear as one of the most innovative drugs used in the management of oral mucositis. Understanding the physiopathological basis of mucositis can lead to the development of target drugs' therapies. In addition, clinical trials should be conducted in order to determine an efficient protocol of treatment.*

**Key words:** Stomatitis; Antineoplastic Agents; Radiotherapy

## INTRODUCTION

Oral mucositis (OM) is defined as an inflammation of oral mucosa resulting from cancer therapy typically manifesting an atrophy, swelling, erythema and ulceration. The condition may be exacerbated by local factors, such as trauma from teeth, or microbial colonization (1, 2).

A biological model for chemotherapy- and radiotherapy-induced oral mucositis proposed by Sonis et al. in 2009, appeared to be generally applicable to alimentary mucositis. What was once thought to be a simple reflection of direct epithelial damage induced by cytotoxic therapy is now considered to be a complex phenomenon that also affects the connective tissue. The model includes events that have been described in five overlapping stages: initiation, upregulation, message generation, ulceration, and healing. All these events lead to pain and, in neutropenic patients, bacteria may invade the systemic circulation causing bacteremia and sepsis. Following cessation of the injurious therapy, healing occurs and the epithelium appears normal again (3).

Chemotherapy-induced mucositis usually develops within 4–7 days after initiation of treatment and peaks within 2 weeks. Radiation-induced mucositis typically begins at cumulative doses of about 15 Gy (after about 10 days) and typically reaches full severity at 30 Gy, and lasts for weeks or even months (1). Patients with oral mucositis are significantly more likely to experience severe pain and weight loss. Severity of oral mucositis has been correlated with compromised swallowing function in patients, resulting in the requirement for feeding via a gastrostomy tube (4, 5).

Development of mucositis depends on a number of factors, related to both therapy and patient characteristics. Some potential risk factors have been identified, while others remain obscure. Treatment variables that may affect the prevalence and the severity of mucositis include the type, dose, and schedule of systemic cytotoxic medications, radiation dose and field, and concomitant use of chemotherapy and radiation. Among patients associated factors, such as, age, body mass index, gender, alterations in salivary production, poor oral health and mucosal trauma

have been reported to influence mucositis. In addition, the tumor itself as well as co-morbidities (e.g. diabetes mellitus, Addison's disease, impaired renal function) may have an impact on mucositis risk. Oral microflora is considered to play a secondary role in the pathogenesis of mucositis. Bacteria colonizing ulcerations may contribute to increased severity and delayed healing (6).

There are no FDA-approved molecularly targeted drugs to prevent gastrointestinal mucositis. Oral and gastrointestinal mucositis therefore continues to represent an important unmet clinical need (5). Few interventions are of proven efficacy in reducing the severity or duration of mucositis, and there are no universally accepted treatment protocols. Many agents and strategies have been used, such as basic oral care, oral rinses, analgesics, cryotherapy, local anesthetics, growth factors and cytokines, biologic mucosal protectants, and anti-inflammatory agents among others. To date, there is not a single treatment capable of preventing or treating mucositis in an efficient way. The purpose of this paper was to present a literature review about the management of oral mucositis.

## MATERIALS AND METHODS

A medical librarian conducted an initial Medline search to identify research articles published between 2005 and 2012 in English language. Pubmed and Scopus were used ([www.pubmed.com](http://www.pubmed.com) and [www.scopus.com](http://www.scopus.com)). A search term combination that included stomatitis, mucositis, lasers, complimentary therapies, amino acids, antioxidants, vitamins, minerals, plant extracts, and cryotherapy was conducted.

## Introduction

Strategies for reducing oral mucositis in order to address this serious impediment to cure have been proven to be inadequate, leaving a very important unmet medical need. The treatments for oral mucositis include: laser therapy, cryotherapy, growth factors, analgesics, mouth washes, administration of antimicrobial agents, vitamins and anti-inflammatory agents.

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### Laser therapy

The continued investigation of new therapies to attenuate oral mucositis for improving both the tolerability and efficacy of the RT in head and neck cancer introduced the low-level laser therapy (LLLT). It is thought to have analgesic, anti-inflammatory, and wound healing effects and no known clinical toxicity (7-11).

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. There have been several positive randomized studies supporting the use of the LLLT in the transplant setting (12).

However, a variety of different technologies, wavelengths and treatment protocols have been evaluated in the head and neck cancer and stem cell transplant populations. However, due to significant variations in study design, technology type, treatment regimen and outcome measurements, comparison across studies is complicated (13).

Laser therapy is an atraumatic, well tolerated by patients and non-invasive technique, which explains why the use of laser in the oral cavity of oncologic patients is increasing. Studies have shown that the LLLT can reduce the severity of oral mucositis and pain (14-16).

The effect produced by the LLLT is based on the capacity to modulate various metabolic processes, by conversion of the laser light energy input through biochemical and photophysical processes, which transform the laser light into energy useful to the cell. Visible laser is absorbed by chromophores in the respiratory chain of the mitochondria, which increases the ATP production that results in increased cellular proliferation and protein synthesis, aiding tissue repair (17).

For analgesia, it has been shown that peripheral nerve stimulation by laser alters hyperpolarization of the cellular membrane, and an increase in the concentration of ATP could contribute to the maintaining of the stability of the membrane and an increase of the pain threshold. Moreover, the LLLT can enhance peripheral endogenous opioid production and decrease serum prostaglandin E2. Pain relief also results in essential improvements of basic oral functions, such as drinking, eating, swallowing, and speaking (18).

### Cryotherapy (Ice chips)

Ice chips' application during chemotherapy infusion, may be effective when concomitant therapy with 5-fluorouracil, is to promote a temporary and localized vasoconstriction on the oral mucosa reducing the exposure of the oral epithelium cells to serum peak levels of cytotoxic agents into the mucosa. In standard radiotherapy protocols, however, this intervention is ineffective (19-21). Oral cryotherapy can significantly reduce oral mucositis in Fluorouracil/Melphalan conditioning allogeneic Stem Cell Transplantation (22, 23).

### Growth factors

#### Granulocyte-macrophage colony stimulating factor

A double-blind placebo-controlled phase III trial reported that subcutaneous granulocyte-macrophage colony stimulating factor (GM-CSF) failed to reduce oral mucositis (24). The results of early-phase trials with the topical application of GM-CSF were encouraging, (25,26), but a prospective randomized trial was negative (27).

### Keratinocyte growth factors

Fibroblast growth factor-7 is an epithelial specific growth factor. The recombinant human form called keratinocyte growth factor (Palifermin - Kevivance; Amgen, Thousand Oaks, California, USA), has also been suggested as having a role to treat OM as it stimulates proliferation and modifies differentiation in epithelial cells, including those of the oral mucosa; hence, this growth factor may be a good candidate for reduction of the mucosal injury caused by radiotherapy or radiochemotherapy (28-30).

Palifermin reduced the incidence and duration of severe oral mucositis in a phase III trial including patients with hematologic malignancies undergoing total-body irradiation with high-dose chemotherapy and peripheral blood stem cell support (31).

A recently reported randomized phase II study evaluated palifermin weekly for 10 doses in patients with locally advanced HNC receiving once or twice-daily RT with concurrent cisplatin/5-fluorouracil chemotherapy (16). Mucositis, dysphagia, and xerostomia were reduced during hyperfractionated radiotherapy (n = 40) but not during standard radiation therapy (n = 59) and not for the combined group. The drug was well tolerated and did not adversely affect survival. It was hypothesized that a lack of consistent activity in this trial was because of the use of a suboptimal dose schedule (i.e., weekly 60 g/kg palifermin). This led to dose-finding studies that confirmed that the dose of 60g/kg, when administered as a single dose, was suboptimal in inducing epithelial cell proliferation as measured by Ki67 staining, but this surrogate endpoint was achieved with higher doses. The evaluation of acute (toxicity) and long-term safety (tumor protection/promotion) for growth factors in mucositis prevention will be required before the use outside of clinical trials can be recommended.

Palifermin was already approved for prevention of oral mucositis in patients undergoing stem cell transplantation for hematologic malignancies (32). A published phase I/II study of palifermin for reduction of mucositis in colorectal cancer patients on fluorouracil-containing regimens demonstrated safety and efficacy in a solid cancer patient population (33).

### Fibroblast growth factors - 20

Valifermin (FGF-20), a member of the same superclass of molecules as palifermin, is also under clinical testing. A number of other growth factor-cytokine- and biological-based therapies are currently in various stages of clinical investigations. It should be noted that some have proposed that growth factors have a theoretical risk of adversely affecting tumor behavior due to the presence of target receptors on cancer tissue (34,35). To date there is no data to support this hypothesis (36).

### Epidermal growth factor

Epidermal growth factor (EGF) is present in various normal tissues and body fluids, including skin, mucosa, tears, cornea, saliva, milk, semen and fluids secreted by the duodenal glands. EGF plays an important role in maintaining tissue homeostasis, as it regulates epithelial cell proliferation, growth and migration. In addition, it has an effect on angiogenesis for the nutritional support of tissues. Thus, EGF has a radical effect on wound healing and tissue generation. Recombinant human EGF (rhEGF)

has been shown to enhance the mucosal wound healing process which suggests that it may be effective in the treatment of radiation induced oral mucositis (37, 38).

### Analgesics and “Magic Mouthwashes”

Topical analgesics include 2% viscous lidocaine and ‘magic’ or ‘miracle’ mouthwash formulations that typically include a combination of lidocaine, benzocaine, diphenhydramine, kaolin, milk of magnesia and/or sucralfate. These agents are swished and expectorated, and can be safely used throughout the day as needed for the duration of mucositis symptoms. Such rinses can be especially beneficial when used prior to alimentation and oral hygiene. Given the presence of opioid receptors in the oral mucosa, topical morphine therapy has been evaluated and shown to be effective in reducing mouth pain; however, it is unclear to what extent the effect is local via peripheral mechanisms rather than systemic via central pathways, especially in the presence of severe ulcerations where transmucosal absorption is quite high (36, 39).

Another combination is antacids, diphenhydramine, and topical antifungal nystatin. They are often with viscous lidocaine in various institutional formulas. Although these are popular, there has been no formal testing of such combinations. Diphenhydramine is sedating and may carry unpleasant anticholinergic properties. Topical nystatin does little to prevent or control candidiasis that may be coexistent with Radiation induced mucositis. Rosenthal et al. in 2009 found that oral ketoconazole or fluconazole are more effective therapeutically for candidiasis in the setting of the RT for head and neck cancer (12).

### Coating agents

There are several mucosal surface protectants available that provide relief by physically coating or soothing the mucosa and decreasing irritation rather than by true analgesic mechanisms. Caphosol (InPharma, Boston, Massachusetts, USA) is a Food and Drug Administration-approved rinse (device) composed of sodium chloride, sodium phosphate and calcium chloride that has been evaluated in the stem cell transplantation population, and shown to be effective in decreasing symptoms of pain and xerostomia. Gelclair (Cambridge Laboratories, Dublin, Ireland) and Mucotrol (Cura Pharmaceutical, Eatontown, New Jersey, USA) are Food and Drug Administration-approved mucoadhesive agents that coat and adhere to the inside of the mouth, and are effective by physically blocking painful exposed nerve endings in the damaged ulcerated mucosa. While safe and generally well tolerated, relief from these agents is variable with additional systemic pain management typically required (36, 40).

### Antimicrobial and antiseptic agents

It is important that patients be monitored closely for signs of oral/pharyngeal infection that may commonly include candidiasis, bacterial, or herpes simplex. A rapid increase in pain, acute exacerbation, or prolonged post-RT mucositis may signify the infection. Patients with such suspicion should undergo culture and sensitivity evaluation and empiric and/or evidence-based antimicrobial therapy. Antimicrobial and antiseptic agents have also been evaluated for their value to prevent mucositis. The use of oral antiseptics has not been fruitful (12).

### Chlorhexidine

Although chlorhexidine gluconate mouthwash is traditionally used in patients with oral mucositis, but there is little evidence to recommend it as a gold standard. While some reports indicate positive effects of chlorhexidine mouth rinse on oral mucositis, recent studies have found either no effect or even negative effects. The bitter taste, dental pigmentation, dysgeusia, and unpleasant sensation experienced together with ineffectiveness provide sufficient reasons for recommending an alternative to the chlorhexidine mouthwash (41, 42).

### Anti-inflammatory agents

Steroidal and non-steroidal anti-inflammatory agents have been the focus of many preclinical and clinical research efforts for mucositis prevention. Disappointingly, betamethasone, prednisolone, and anti-inflammatory prostaglandins E1 (misoprostol) and E2 (Prostin, Pfizer, NY, NY) did not reduce HN RIM or chemotherapy stomatitis in clinical trials (43-46).

### Benzydamine

Benzydamine hydrochloride is a non-steroidal agent, a unique topical agent with anti-inflammatory, analgesic and antimicrobial properties, which is utilized extensively for prevention of radiation-induced mucositis in Europe and other parts of the world (47). A published phase III trial evaluated the primary endpoint of the efficacy of benzydamine to reduce mucositis at 50 Gy. This endpoint was reported positive, but there was no efficacy data beyond that limited dose and no difference in pain on swallowing (48). Most recently, a study in India concluded that benzydamine is well tolerated and helps reduce the pain and severity of oral mucositis (49).

### Amifostine

Amifostine (WR-2721) is the FDA approved to decrease the rates and severity of both acute and chronic xerostomia. The impact of amifostine on head and neck mucositis when used at traditional xerostomia prevention doses is less clear. It is another option for use with ionizing radiation for maintaining salivary flow, but it has some significant side-effects and its effects on salivation are moderate. However, if used subcutaneously, the side-effects are minimal (50).

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. Multinational Association of Supportive Care in Cancer and National Comprehensive Cancer Network guidelines do not make any recommendation for or against the use of amifostine for mucositis prevention during head and neck RT (51). While effective in reducing acute and long-term salivary gland hypofunction secondary to head and neck radiation, amifostine (Ethylol; MedImmune, Gaithersburg, Maryland, USA), a free radical scavenger, has not consistently demonstrated efficacy in the prevention of mucositis although clinical studies are ongoing (52).

### CONCLUSION

Studies have shown a lot of therapeutic strategies to prevent and treat oral mucositis, such as laser therapy, cryotherapy, growth factors, analgesic, mouth washes, antimicrobial agents, vitamins and anti-inflammatory

agents. Growth factors, including palifermin, appear as one of the most innovative drugs used in the management of oral mucositis. A better understanding of the physiopathological basis of mucositis can lead to the development of new target drugs' therapies. In addition, clinical trials should be conducted in order to determine an efficient protocol of treatment.

### Conflict of interest

We declare no conflicts of interest.

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