Current Topical Trends and Novel Therapeutic Approaches and Delivery Systems for Oral Mucositis Management

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Oral mucositis (OM) is an extremely serious and challenging complication of chemoradiotherapy, which may limit the efficacy of cancer treatment. Complications related to OM include potential nutrition impairment, high economic burden, and negative impacts on patients’ quality of life. Current therapeutic options with local traditional pharmaceutical formulations are largely focused on controlling symptoms, and only few agents are available for treatment. Several local supportive and palliative agents are used for the prevention of OM; however, a standard treatment for the disease has not been confirmed yet. The efficacy of treatment could be improved through the introduction of new medical agents with updated dosage forms that can enhance and optimize local drug delivery and create greater therapeutic effects with fewer side effects. The focus of this review was to provide clear and direct information about the currently available topical therapeutic agents in clinical practice used to cure and/or reduce the incidence of ulcerative symptoms of OM, excluding the associated pain and other coexisting complications such as bacterial and fungal infections. The review also provides recent evidences regarding agents that could be used as promising novel therapies in updated local delivering systems. This will support further encouraging options and approaches for the management of OM and will improve compliance that could be translated in better disease control and survival.

**Keywords:** Chemotherapy, mucoadhesive films, oral mucositis, radiotherapy, topical therapy

**INTRODUCTION**

The oral mucosa is known to have a high rate of deoxyribonucleic acid (DNA) synthesis and fast turnover, which renders it highly susceptible to the toxic effects of chemoradiotherapy; both are widely used interventions in cancer treatment. Oral mucositis (OM) is considered as the most significant, major debilitating, and unavoidable side effect of chemoradiotherapy. It affects 20%–40% of patients treated with conventional chemotherapy, approximately 80% of patients receiving high-dose myeloablative chemotherapy before hematopoietic stem cell transplant and up to 100% of patients undergoing radiotherapy for head and neck cancer.\(^1\)–\(^3\) The inhibition of cell division results in mucosal atrophy followed by ulceration of the mucosal barrier alongside the release of inflammatory cytokines from the epithelium and connective tissue. Therefore, local damage of the oral mucosa associated with inflammatory response may give rise to the OM.\(^4\) The incidence of OM is increased by concurrent chemotherapy, particularly with the administration...
of 5-fluorouracil (5-FU) with or without folinic acid, doxorubicin, etoposide, vinblastine, taxanes, and methotrexate. of 5-fluorouracil (5-FU) with or without folinic acid, doxorubicin, etoposide, vinblastine, taxanes, and methotrexate. OM is associated with significant pain, odynophagia, dysgeusia, dehydration, malnutrition and a decline in speaking function, general oral health, and quality of life. These complications have a more economic burden as they increase the risk of infection and increase morbidity and mortality rate. In addition, it is a leading cause for therapeutic dose reduction, restrains on the delivery of optimal cancer therapy protocols, and premature cessation of treatment for both chemoradiotherapy. All these can directly diminish cure rates and treatment outcomes and negatively impact the survival rate and patients’ quality of life. For the prevention and treatment of OM, the oral cavity is a potential site for local delivery of therapeutic agents. Oral mucosal drug delivery promoted a more convenient, reliable and efficient method for the delivery of smaller amount of drug than systemic drug delivery. This will also reduce systemic side effects. Moreover, oral mucosa is easily accessible, and this type of drug delivery provides drugs to be self, easily administered and well accepted by patients. However, there is an actual need for the development of more effective treatment strategies for OM. The current strategies are primarily topically applied agents, which are considered as empirical, palliative, and supportive and also require dose repetition to obtain a favorable therapeutic effect.

**Current Trends for Prophylaxis and Treatment of Oral Mucositis**

**Anti-infective mouth rinses**

Sodium bicarbonate shows an efficacy in managing OM through preventing progression of infection. This is achieved via its antiseptic properties or inhibiting some inflammatory triggers in the oral cavity. It also dilutes accumulating mucus, provides deodorizing, and buffering activities alongside neutralizing the elevated mouth acidity. Treatment with this topical mouthwash has the advantages of comfortable preparation at home by the patient themselves and low economic burden. However, this mouthwash is not free from disadvantage, which is relating primarily to salty unpleasant taste that could affect patient adherence. Earlier literature has reported the efficacy of this topical mouthwash as an effective intervention for chemoradiotherapy-induced OM, whereas others found conflicting results with no clear evidence of benefit. Chlorhexidine is an effective topical broad-spectrum anti-plaque antiseptic agent. It can improve oral hygiene with a reduction of potential gram-positive and gram-negative bacterial pathogens (bactericidal), fungal yeasts (fungicidal), and prevent dental plaque accumulation and moderate to severe gingivitis. Its main unwanted side effect is reversible discoloration of teeth, tongue, and mucous membranes. Many clinical studies reported that chlorhexidine 0.12% and 0.2% mouthwashes are effective in reducing the incidence of chemotherapy-induced OM in children and adults; however, its use in radiotherapy-induced OM is unproven, and the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) guidelines recommend against its application for prevention or treatment of radiotherapy-induced OM.

Another anti-infective mouthwash is benzydamine, a nonsteroidal anti-inflammatory agent that inhibits pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β. In addition, it has antimicrobial, anesthetic, and analgesic properties. It is reported to be useful in controlling topical pain and reduced opioid intake, making it suitable for use in both prevention and treatment of OM. Its use is associated with the occurrence of initial severe oral stinging, which decreases patient compliance, requiring the usage of additional topical anesthetics. The MASCC/ISOO guidelines recommended its use for reducing the severity of OM in patients with head and neck cancer, receiving moderate-dose radiotherapy (up to 50 Gy) without concurrent chemotherapy. However, the beneficial effect of benzydamine seems to be questionable in chemotherapy-induced OM. Povidone–iodine (PVP-I) oral mouthwash remains a popular, easy, cheap, safe, and efficacious agent in clinical settings for the treatment of inflammatory symptoms of OM. PVP-I has anti-microbial activities achieved through the inhibition of cellular mechanisms via the oxidation of nucleotides, amino acids and fatty acids in cell membrane. PVP-I shows antiseptic, anti-inflammatory, anti-edematous, and anti-hemostatic effects. It has broad-spectrum antibacterial, antifungal, and antiviral effects. In addition, it suppresses TNF-α release, reduces β-galactosidase activity and produces inhibitory effect on leukotriene B4, and leukocyte extravasation. However, the MASCC/ISOO guidelines note that studies regarding the use of PVP-I mouthwash still are inadequate or with conflicting data in the treatment of OM.
in reducing the incidence and severity of OM and associated oral pain by restoring the natural electrolyte and pH balance of salivary fluid and by moistening and lubricating mucosal tissues of the oral cavity. [29,30]

**Anti-ulcerative medications**
Sucralfate is a basic albumin salt of sucrose octasulfate. As a coating local agent, it forms a cytoprotective physical barrier over the ulcer, induces prostaglandin and mucus production, increases mucosal blood flow, increases growth factor binding, and produces antibacterial activity, which accelerate wound healing. [31] Topical use of sucralfate may reduce local pain during feeding alongside a reduction in the use of topical anesthetics or systemic analgesia. [32,33] However, conflicting results are reported regarding its efficacy with limited beneficial effect for the prevention of chemotherapy-induced OM. [34] On the contrary, hydroxypropyl cellulose, sodium alginate (ALG), and polyvinylpyrrolidone-sodium hyaluronate gel are considered as bioadhesive film-forming or coating agents that serve as a protective barrier over mucosal ulceration, allowing relief of oral pain, improving oral ulcer discomfort, and healing for at least 3 h post application for chemotherapy-induced OM. [35,36]

**Anti-inflammatory agents**
Dinoprostone is a prostaglandin-E2 (PGE2), naturally occurring as a cytoprotective agent. As inflammation is an important component in the incidence of OM, topical application of dinoprostone has been shown to be effective in reducing chemoradiotherapy-induced OM. [37] However, complete evidence of a clear therapeutic benefit is further required. One of the most important anti-inflammatory agents is glutamine. It is a free primary amino acid precursor for protein synthesis, which is involved in cell replication of the gastrointestinal mucosal cells. It has a remarkable anti-inflammatory and antioxidant properties that could help decrease mucous membrane injury and assist recovery of oral mucosal cell damage. In carcinomas, massive glutamine depletion could be developed over time, and this negatively impacts the optimal function of host tissues that are relied on adequate glutamine stores. [38-40] Glutamine significantly reduces the oral pain, maximal grade, duration, and severity of OM in patients receiving chemoradiotherapy. The local administration of glutamine results in direct absorption by the oral mucosal cells where the inflammatory response is altered by a reduction in pro-inflammatory cytokine production and cytokine-related apoptosis. This modulation in the inflammatory response increases fibroblast and collagen synthesis and decreases mucous membrane injury. The ultimate result could provide recovery from mucosal damage and promote healing of oral mucosal tissue. [41-43]

**Antioxidants**
Vitamin A exerts significant inhibitory effects on inflammation and epithelial proliferation, produces temporary cell cycle arrest of oral epithelium, and enhances mucosal resistance to cycle-specific cytotoxic treatment. The prophylactic use of topical tretinoin has been found to reduce oral complications during bone marrow transplantation. [44] Meanwhile, vitamin E exerts antioxidant properties and membrane-stabilizing potency, limits reactive oxygen species (ROSs) and free radicals release during inflammation, which mediates tissue damage, thus diminishes the severity of OM. It seems that topical application of 100 mg of vitamin E twice a day could lead to the disappearance of oral lesions and treat the established ones. [47] It has been found that direct application of allopurinol mouthwash brings the drug in direct contact with the inflammation site at higher concentration allowing the free radical scavenger effects of allopurinol to inhibit superoxide dismutase activity and suppress proteases. In addition, allopurinol metabolite, oxypurinol, inhibits an enzyme involved in pyrimidine synthesis, leading to intracellular accumulation of orotic acid. The high level of orotic acid diminishes 5-FU toxicity and could provide prophylaxis of 5-FU-induced OM. [48,49] Although allopurinol mouthwash is simple and effective, it is not stable for long-term preservation, and it is difficult to control the amount of allopurinol during gargling. [50] Another important agent that belongs to the group of salivary function modifiers is pilocarpine, a topical cholinergic agonist, which showed efficacy in preserving salivary gland function and relieving symptoms of radiotherapy-induced OM. [51]

**Cytokines and growth factors**
Both granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) belong to a family of glycoprotein growth factors. They promote the proliferation and differentiation of neutrophils and macrophage precursors of the oral mucosa and improve chemotaxis, phagocytosis, and intracellular oxygen metabolism of neutrophils. Through these mechanisms, recovery of peripheral blood neutrophil counts is achieved, and the migration of neutrophils to the oral cavity contributes to the reduction of neutropenia, infection rate, and consequently reduced duration and severity of OM. [52,53] Their topical mouth rinse administration is associated with a high reduction rate in the incidence and duration of chemoradiotherapy-induced OM, particularly with doxorubicin, ifosfamide,
Topical application of transforming growth factor-beta (TGF-β) to the oral mucosa results in a significant reduction in basal cell proliferation, leading to reduced incidence, severity, and duration of chemotherapy-induced OM. Despite these effects, controlled clinical trials have to be performed to further show the efficacy of TGF-β.

Cryotherapy

It is a local ice cooling process of the oral mucosa that could support the delivery of optimal chemotherapy. The process can cause temporary vasoconstriction, thus reducing the delivery of chemotherapy to the oral mucosa. Cryotherapy is only useful for short bolus chemotherapy infusions with no significant role in radiotherapy-induced OM. It has been found that placing ice chips in the mouth 5 min before administration of chemotherapy, replenished as needed for up to 30 min, decreases the delivery of the chemotherapeutic agent to the oral mucosa. The MASCC/ISOO guidelines alongside several studies have shown that cryotherapy reduces the severity of OM in patients receiving bolus doses of chemotherapeutic agents, particularly those receiving bolus doses of 5-FU, melphalan, and edatrexate.

Low-level laser therapy

LLLT also called photobiomodulation therapy (PBMT) is a non-invasive care involves a simple application on oral mucosa of a high-density monochromatic narrow band light source with various wavelengths (630–830 nm). When applied locally, it exerts potential effects on ROSs and/or pro-inflammatory cytokines (TNF-α, IL-6, and IL-8); all contribute to the pathogenesis of OM. On the basis of the proposed mechanism, LLLT could be used to prevent symptomatic OM induced by chemotherapy. Multiple studies reported significant reduction in the severity of oral pain, dysphagia, need for opioid analgesia, and therapy interruptions with the application of LLLT with no notable side effects.

Novel approaches for oral mucositis management: trends of medical agents and dosage forms

Although mouthwashes are frequently used in the treatment of OM, they are considered to have a limited action because of the short contact time with mucosal tissues. In addition, the act of gargling is extremely difficult because patients with OM usually experience episodes of severe pain, which will reduce the efficacy of the pharmaceutical formulation used.

Local delivery is considered as a simple pathway in terms of easy application, and it prolongs drug contact time with oral and pharyngeal mucosa. However, drug delivery through this route is quite challenging because of the relative impermeability of the oral mucosa, the mechanical stress induced by the oral cavity functions, the wash away effect of the saliva, and the environmental and enzymatic conditions. This requires the development of efficient local delivery systems that can enhance favorable drug penetration and retention, thereby increase contact time with mucous tissues, reduce number of doses given, and minimize possible side effects.

Among these novel approaches is rebamipide. It has a variety of pharmacological properties, including promotion of PGE2 synthesis, upregulation of epidermal growth factor and its receptor, induction of mucus secretion, antioxidant activities, and inhibitory effect on inflammatory cytokine production. Previous literature reported the efficacy and safety of rebamipide mouthwash in the prevention of chemoradiotherapy-induced OM. However, the local concentration of rebamipide on the oral mucosa cannot be maintained, and the protective effect has a short residence time in the oral cavity. An experimental study conducted on poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles, which were coated with chitosan hydroxypropyltrimonium chloride, were prepared as carrier systems of rebamipide for therapeutic effectiveness on chemotherapy-induced OM. These nanoparticles were evaluated using a mouse model and significantly decreased oral ulcer area and treatment duration in comparison to control group, suggesting that rebamipide-loaded PLGA nanoparticles, coated with chitosan hydroxypropyltrimonium chloride, are a beneficial strategy for the treatment of chemotherapy-induced OM. The local use of nonsteroidal anti-inflammatory drugs (NSAIDs) is found highly useful in the treatment of stomatitis and oral ulcers. Several new dosage forms have been developed to improve oromucosal delivery of NSAIDs, such as mucoadhesive films, proniosomal gels, liquid crystalline films, and buccal tablets and electrospun nanofibers (NFs). The best example is mucoadhesive buccal ketoprofen (KET) and electrospun NFs, which is developed experimentally and evaluated in animal models for pain and inflammation management of OM as an alternative dosage form to orally administered KET.

Topical treatment using film dosage forms has been reported to be useful for OM because it can protect oral mucosa and control the release of drugs from oral mucosal drug delivery systems. A film dosage form of...
allopurinol is prepared and anticipated to be useful as a simple dosage form in oral care, particularly in patients with swallowing difficulties in chemoradiotherapy-induced OM. This dosage form is prepared using water soluble polymer bases for immediate dissolution in saliva. The homogenous presentation of allopurinol throughout the FD allows its spreading in the oral cavity following its disintegration.[77,78]

Ginsenoside Rb1 has well-known biological activities such as anti-ulcer effects and burn wound healing.[79,80] In an experimental study, ginsenoside Rb1 was isolated from ginseng and contained in chitosan-sodium alginate (ALG) mucosal adhesive films (G-Rb1 film).[81] These films were attached to the oral mucosa to evaluate the effect of ginsenoside Rb1 on 5-fluorouracil-induced OM. The results of this study found that topical application of ginsenoside Rb1 mucosal adhesive films has anti-inflammatory properties and healing effects on severe OM induced by chemotherapy. An interesting natural product designed to be of importance in the treatment of OM is propolis, a resinous material enriched with natural compounds such as polyphenols, flavonoids, phenolic aldehydes, amino acids, and steroids. It shows a broad-spectrum antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory action making it useful in the treatment of various oral conditions.[82-84]

In this regard, a clinical study was performed using a mucoadhesive gel containing 5% wt/vol green propolis to determine its effectiveness in the prevention of radiotherapy-induced OM.[85] Patients are instructed to apply this mucoadhesive gel three times daily starting the day before the radiotherapy course and continue for 2 weeks with weekly follow-up for evaluation of food intake, pain, and grading of mucositis. At the end of the study, the results showed that the majority of patients did not develop mucositis. Moreover, all patients did not report any symptoms of oral pain, oral infection, or discontinued food intake. These findings suggest that this gel could be considered as a promising and potential topical medication for preventing radiotherapy-induced OM.

Moreover, a double-blind, randomized prospective clinical trial was performed using localized higher concentration of triamcinolone acetonide and licorice mucoadhesive films for the management of OM during head and neck cancer radiotherapy,[86] and they were designed to remain in the mouth for a long period through adherence to the mucosal tissues. The developed mucoadhesive films showed promising results for pain control and OM treatment associated with radiation therapy. Another double-blind, randomized, placebo-controlled study was also performed using a mucoadhesive hydrogel (MuGard). It is a viscous mucoadhesive hydrogel oral liquid formulation that forms a palliative mucoadhesive barrier over injured mucosa when applied and shows good results in mitigating OM symptoms and delaying OM progression tolerability and safety in chemoradiotherapy.[87] It has been found that melatonin could play an important role in normal oral physiology. It shows immune system protection and radioprotective effects related to multiple functions, including antioxidant properties and reduction of DNA damage, lipid peroxidation, and apoptosis.[88,89] On the basis of this, the treatment with melatonin gel plays a beneficial role in the prevention of mucosal disruption and can protect from radiotherapy-induced OM in head and neck cancer.[90]

**Conclusion**

OM is a clinically debilitating and dose-limiting complication of cancer therapy. Several supportive and palliative treatments are already available in the clinic. However, a standard treatment for the disease has not been confirmed yet, and its management is mainly through mouthwashes. The efficacy of the treatments could be improved through the introduction of different dosage forms that can enhance and optimize local drug delivery and create greater therapeutic effects with fewer side effects.

**Ethical approval**

Approval of the study was granted from the ethics committee of College of Pharmacy, Mustansiriyah University, Baghdad, Iraq. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. For this type of study, formal consent is not required.

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**Conflicts of interest**

There are no conflicts of interest.

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