

Oral Mucositis in Cancer Care: Current Insights and Future Directions from a Systematic Review

Deepak Kumar Jha, S. Manasa, Kusu Susan Cyriac, Raveena Shree R*

Department of Pharmacology, Karnataka College of Pharmacy, Thanisandra Main Rd, Chokkanahalli, Bengaluru, Karnataka, INDIA.

ABSTRACT

Oral Mucositis (OM) is a painful inflammation often resulting from cancer therapies like chemotherapy and radiotherapy. OM manifests as ulcers that can make eating and speaking difficult and increase infection risk. Current management primarily involves clinical assessment and patient reports, but biomarker discovery is underway to improve diagnostic accuracy and treatment monitoring. Emerging biomarkers associated with inflammation, oxidative stress, and tissue repair could help assess OM severity and therapeutic efficacy. Emerging treatments for OM focus on cell-based therapies, like mesenchymal stem cells, exosomes derived from MSCs, epithelial stem cells, HSCs, and immune cell therapies that offer anti-inflammatory benefits and promote tissue repair, potentially accelerating mucosal healing. Platelet lysate, rich in growth factors, has shown promise in reducing inflammation and aiding regeneration, especially in formulations such as *in situ* gelling sprays. These advancing personalized treatment approaches, potentially reducing complications, aim to improve patient outcomes by enhancing healing, reducing pain, and lowering infection risk.

Keywords: Biomarkers, Cell-based therapies, Chemotherapy, Healing, Immune cells, Inflammation, Oral Mucositis, Radiotherapy.

Correspondence:

Mrs. Raveena Shree R

Department of Pharmacology, Karnataka College of Pharmacy, Thanisandra Main Rd, Chokkanahalli, Bengaluru, Karnataka, INDIA.

Email: raveenashree@gmail.com

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INTRODUCTION

Oral Mucositis is a common and often debilitating condition characterized by inflammation and ulceration of the mucous membranes in the oral cavity, primarily affecting patients undergoing cancer therapies such as chemotherapy, radiation, or HSCT (Kamulegeya *et al.*, 2021). The severity of Oral Mucositis can significantly affect patients' quality of life, leading to pain, difficulty eating and speaking, increased risk of infections, and potential interruptions in cancer treatment. Non-surgical cancer treatments including chemotherapy and radiotherapy can have a toxic side effect known as oral mucositis, which can cause substantial pain and impede eating and swallowing are fundamental physiological demands (Kusiak *et al.*, 2020). A mucosal lesion caused by inflammation has developed due to chemotherapy or radiation therapy (Singh, V and Singh, A.K, 2020). The occurrence of mucositis throughout the GIT, ranging from the mouth to the anus, can present a challenge to the patient and oncologist due to the varying symptoms (Brown and Gupta, 2020). A characteristic of OM is an inflammatory reaction that manifests clinically in erythematous and/or ulcerated lesions,

preferentially on the mucosa of the buccal cavity, the lingual dorsum, palatal region and mouth's bottom (Farias *et al.*, 2021). The initial lesions typically start as an erythema, which can develop into erosive and/or ulcerated lesions (Farias *et al.*, 2021). It is considered to be the most serious non hematological condition of cancer treatment (Chaveli-Lopez B and Bagan-Sebastian, 2016). Chemotherapy has been associated with mucositis in up to 40% of patients with cancer; while radiotherapy is associated with mucositis in the majority of individuals with head and neck cancer, up to 80% (Singh, V and Singh, A.K, 2020). Apoptosis could contribute to the emergence of Oral Mucositis caused by chemotherapy and radiotherapy (Plevova, 1999). When mucositis is severe, anticancer treatment may be interrupted or scaled back, which has a negative impact on oncologic results. Severe mucositis can also be compounded by uncontrolled pain, superinfection or a systemic infection, the bleeding, and dehydration (Farias *et al.*, 2021). numerous cytokines involved in inflammation and wound repair are known to express themselves more often in response to ionizing radiation. The prognosis has also been linked to cytokine levels in tumours and circulating cytokines (Citrin *et al.*, 2012). The inflammatory and immune responses caused on by injury or infection are commonly detected by acute phase reactants (Ki *et al.*, 2009). Oral issues can be categorized into two (2) types: an acute and late complication, acute complications are associated to occur during therapy or treatment while late complications occur after therapy. Acute complications of radiation therapy for



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the head and neck area can comprise sialadenitis, oropharyngeal mucositis, xerostomia, fungal and viral infections, taste dysfunction, and mucosal fibrosis and atrophy. Late consequences may include taste dysfunction, tissue necrosis, xerostomia, and dysphagia and mucosal fibrosis (Singh, V and Singh, A.K, 2020).

Key Aspects of Oral Mucositis

Mucositis Pathogenesis

Oral mucositis arises from complex biological mechanisms triggered by cancer treatments, particularly chemotherapy and radiation. One of the primary effects is epithelial damage, as cytotoxic drugs and radiation directly harm the rapidly dividing basal epithelial cells, leading to the breakdown of the mucosal lining. This damage initiates a robust inflammatory response, with the release of pro-inflammatory cytokines, which further contribute to tissue injury and the formation of painful ulcers. Additionally, the compromised mucosa becomes vulnerable to bacterial invasion, allowing microbes to enter and worsen the inflammation. The healing process is also impaired, as ongoing cancer treatments delay tissue regeneration, further complicating the recovery of the damaged oral tissues. Oral mucositis caused by chemotherapy and/or radiation therapy can be classified into two main mechanisms: direct and indirect mucositis. Direct mucositis: The oral mucosa's epithelial cells experience frequent turnover, typically per 7 to 14 days, making them vulnerable to the effects of a cytotoxic therapy. Radiation therapy and chemotherapy both alter normal cell turnover and cause cell death by interfering with the maturation and cellular development of epithelial cells. Indirect mucositis: Mucositis that is brought on indirectly by gram-negative bacteria and fungi is known as indirect mucositis. When patients are neutropenic, they become more susceptible to oral infections, which often arise as a result of indirect stomatotoxicity. This condition occurs when cancer treatments, such as chemotherapy or radiation therapy, damage the oral mucosa, leading to an increased risk of microbial invasion. The compromised mucosal barrier allows pathogens to enter more easily, resulting in infections that can exacerbate oral health issues. Additionally, the reduced neutrophil count diminishes the body's ability to fight off these infections, making it crucial for healthcare providers to implement preventive measures, monitor oral health closely, and manage any signs of infection promptly. Effective oral hygiene practices and the use of prophylactic antimicrobial agents can help mitigate the risk of oral infections in neutropenic patients. Depending on the time of the neutrophil linked with the chemotherapy agent delivered, the onset of mucositis owing to myelosuppression varies, but commonly manifests 10 to 21 days after chemo delivery. These indirect effects further contribute to the development and severity of mucositis, making it a multifactorial condition (Naidu *et al.*, 2004).

Stages of Mucositis

The 4 phases of the mucositis mechanism are as follows:

Initial inflammatory/vascular phase, Phase I: IL-1B (Interleukin-1B), Prostaglandins (PG) as well as TNF (Tumour Necrosis Factor) are few examples of proinflammatory cytokines that are released during this phase by exposed cells in the buccal mucosa, including epithelial, endothelial, and connective tissue cells. These inflammatory mediators increase vascular permeability, which enhances the uptake of cytotoxic drugs into the oral mucosa and causes further harm either directly or indirectly.

Nuclear Factor-kB (NF-kB) and p53 are activated by cellular injury, which is perhaps the most important event in the damage response and considered to be the primary response. IL-1b, IL-6, and Tumour Necrosis Factor are three inflammatory cytokines produced as a result of NF-kB activation, which ultimately causes tissue damage and cell death. Mucositis can continue to be subclinical or barely noticeable at this point it leads to signal amplification (Brown and Gupta, 2020).

Epithelial phase, Phase II: During this stage, chemotherapy and/or radiation slow down the oral mucosal epithelium's cell division, which reduces epithelial renewal and turnover and ultimately causes epithelial collapse. 4 to 5 days after the start of chemotherapy, this causes erythema from increased blood flow and epithelial atrophy. At this point, ulceration results from microtrauma brought on by regular actions including talking, swallowing, and mastication.

Phase III: Ulceration: The clinical manifestation of cellular injury; ulcers in the mucosa may be visible. At this point, there is a high danger of bacterial colonization and sepsis developing (Brown and Gupta, 2020).

Bacteriological/ulcerative phase (Pseudomembranous) within a week of therapy, epithelial breakdown leads to the ulcerative stage, which is the final stage. Pseudomembranous and ulcers develop as a result of epithelium loss and ferocious exudation. During this stage, yeast and Gram-negative bacteria start to colonize the injured mucosal surfaces, which may be made worse by the presence of concurrent neutropenia. One of the most difficult elements of severe myelosuppressive antineoplastic medication therapy is managing infectious problems that develop in neutropenic transplanted bone marrow recipients. Numerous studies have shown the significance of ulcerative mucous inflammation as an underlying cause of systemically a-hemolytic infections caused by streptococcal in neutropenic cancer patients.

Phase IV: The phase of recuperation usually lasts 12 to 16 days, this phase's duration is mostly influenced by the pace of epithelium proliferation, hematopoietic repair, the regrowth of the localized microbiological plant life, and the absence of factors

like infections and mechanical irritation that might delay wound healing (Naidu *et al.*, 2004).

Chemotherapy-Induced Oral Mucositis (CIOM) and Radiotherapy-Induced Oral Mucositis (RIOM)

CIOM and RIOM have distinct but overlapping mechanisms. Both types share similar clinical outcomes but vary in their onset, duration, and underlying cellular damage. Managing OM effectively requires understanding these distinctions to tailor prevention and treatment strategies based on the type of therapy patients receive. The both treatments initiate cellular damage to epithelial damage and generate ROS damaging cells. But there is slight difference in clinical course of OM induced by radiotherapy versus chemotherapy, with chemotherapy mucositis onset is typically 4 to 7 days after 1st dose and present with erythema. Symptoms peak during first 2 weeks of treatment and resolve within 2 to 4 weeks of chemotherapy cessation. The onset of radiotherapy induced OM is dose dependent, but symptoms are often evident at the end of first week. At a cumulative radiation dose of 30 Gy, the peak severity of lesions is seen, primarily on non-keratinized tissue within the field of radiation, but also on keratinized surfaces. Oral mucositis may last from 2-6 weeks after radiotherapy has been concluded, but in some cases, it may persist for several months. Patients receiving both chemotherapy and radiotherapy may experience an earlier onset, increased severity, and a longer duration of oral mucositis. Patients who receive radiation therapy or chemotherapy at a high dose for hematopoietic stem-cell transplantation often experience Oral Mucositis as the most distressing side effect of myeloablative therapy (Christin Melton. ELS, 2017). In individuals receiving chemotherapy, mucositis occurs in around 40% of cases; in patients with head and neck cancer receiving both chemo and radiation, it occurs in about 90% of cases (Pulito *et al.*, 2020).

Risk factors

An individual patient's likelihood of developing mucositis varies on a number of variables, including the particular chemotherapy or radiation modality employed as well as the dosage, frequency, and length of treatment (Brown and Gupta, 2020). Oral mucositis risk factors can be categorized into patient and treatment-associated groups. Despite the tumour itself, though, can be quite important. Drug selection, prospective the adjuvant drug use, and the type, dose, and duration of chemotherapy or radiation therapy are all factors associated to treatment. Older age, higher BMI, mouth surroundings, and inherited characteristics are elements that are specific to the patient (Kusiak *et al.*, 2020). Smoking, poor dental hygiene, being younger, being a woman, having a female partner, having a nutritional pretreatment status, and having pretreatment neutrophil counts are all factors that may affect a patient's chance of getting mucositis and its severity (Brown and Gupta, 2020). The fact that female patients experience a higher probability of developing Oral Mucositis from methotrexate and

5-FU medication speaks volumes about the importance of the feminine gender (Kusiak *et al.*, 2020).

The key categories into which the risk factors were divided were as follows

- A. Chemotherapy medications.
- B. Underlying illness.
- C. Particular people.
- D. Hematological, hepatic, renal parameters.
- E. Biomarker variables and genetic profiles.
- F. Oral microbiota variables.

Chemotherapy drugs/agents

Chemotherapeutic drugs were mostly listed as risk factors in the study by De Farias Gabriel *et al.*, 8 of the 19 studies (42% of them) suggested that the use of chemotherapeutic drugs could increase the chance of developing OM. High dosages of MTX individually were found to be a significant risk aspect for the onset of OM, with a plasma concentration of 0.2 mmol/L of MTX66h in the trial. A few particular procedures and each chemotherapy substance for the treatment of some neoplasms for the therapy of Hodgkin lymphoma, for example, COG AHOD0031 and COG AHOD0831, leukemias, Burkitt lymphoma, Acute lymphoid leukemia and the Ewing's sarcoma, Vincristine, ifosfamide, doxorubicin, etoposide, misulban, melphalan, cisplatin, and multidrug conditioning regimen. Cyclophosphamide, vincristine, prednisone, methotrexate, and doxorubicin, busulfan, MTX, and cytarabine were also mentioned as potential risk factors, along with other substances like daunorubicin, doxorubicin, vincristine, and etoposide.

The underlying illness

Considering underlying illness being susceptible to OM Hematological malignancies, Acute Myeloid Leukaemia, Hodgkin lymphoma, and Non-Hodgkin Lymphoma. Diagnoses of solid tumours including germinal tumours and undifferentiated nasopharyngeal carcinoma were documented, and cancers such as acute leukaemia, solid tumours, and lymphoma were considered to be additional OM risk factors.

Individual characteristics

Such as low body weight, illness, preceding OM, elevated anxiety, and OM on days 8 and 9 of chemotherapy cycles are examples of personal traits.

Regarding hematological parameters

Neutropenia, a WBC counts below 9,500 mm³, a low number of lymphocytes in patients with solid tumours, high levels of platelet mm³ and low levels of platelets are all possible OM risk factors.

In addition to being linked to OM, elevated levels of indirect and total bilirubin, creatinine, and alanine aminotransferase and aspartate aminotransferase have also been found to enhance the risk of OM.

Identified biomarkers and genomic variations as OM predictors

The human MDR1 gene expresses a protein that controls the flow of several chemotherapeutic drugs in malignant neoplasms. One known risk factor for OM is the MDR1 gene mutation c.3435C>T, which has a CT genotype.

ATP-binding cassette subfamily C member 4 is an important ABC transporter gene, encoding a protein that confers drug resistance and facilitates the removal of chemotherapeutic medications like MTX. The ABCC4 gene variant rs7317112 was discovered to belong to an AA genotype, which possessed was linked to a greater risk of getting OM. The gene XRCC1 encodes protein that repairs DNA which functions to repair DNA damage caused by oxidative stress, ionizing radiation, and alkylating substances. The Arg194Trp and Arg399Gln polymorphisms in XRCC1 have been associated with a higher risk of cancer, and the 399Gln allele of this gene raises the possibility of having severe OM. In contrast, the 194Trp allele was found to have a protective effect against OM. Analysis of patients with acute leukemia showed that increased levels of pro-inflammatory cytokines and reduced levels of the antimicrobial protein proLL-37 were associated with higher OM levels (Farias *et al.*, 2021).

Additionally, important in the occurrence of Oral Mucositis are genetic variables. First off, genes have an effect on how chemotherapeutic drug-metabolizing enzymes function. For example, a deficiency in dihydropyrimidine dehydrogenase would raise the likelihood of 5-FU toxicity. However, recognized enzyme deficits with reference to a propensity to Oral Mucositis are uncommon (Kusiak *et al.*, 2020).

The risk of getting OM may be increased by changes in the oral microbiota, which HSV-1, the type 1 herpes simplex virus, has been associated with Oral Candida spp and unspecified bacterial infections have been identified as predictors of OM. Furthermore, discovered as an early indicator of OM was oral *candida* ssp. Another description of OM risk factor included unspecified infections caused by bacteria (Farias *et al.*, 2021).

Grading of mucositis

The Mucositis Score is used to assess and evaluate the level of toxicity caused by a certain treatment or medication (Scully *et al.*, 2004). The type of mucositis and its severity can vary on treatment dose, the size of the exposed area, and the fractionation strategy. It also appears to be regulated by a variety of molecules, including EGF and TNF-alpha, indicating as mucositis is not only an epithelial condition (Normando *et al.*, 2017). The clinical signs and symptoms of Oral Mucositis can range from mild

lesions and ulceration to mucosal erythema. The World Health Organization, or WHO scale is the most commonly employed scale to assess Oral Mucositis symptoms in both research and clinical application (Kusiak *et al.*, 2020) (Tables 1 and 2).

The National Cancer Institute (NCI) created a different scale that divides into clinical examinations and symptoms (Kusiak *et al.*, 2020) (Table 3).

Oral examination was used to assess the frequency and seriousness of OM by WHO's oral toxicity scale, Common terminology criteria for AEs like patient self-administered questions reported discomfort in the mouth, throat, or evaluation scale. Quality of Life (QoL) assessment was done through valid questions by interviewing them face to face, the most often utilized questionnaires were OMQoL, EORTC-QOL-C30, FACT-G, MQoLS-CA, and OMDQ are the few scales used for assessing Oral Mucositis incidence and its severity acc to grade (Al-Rudayni *et al.*, 2020).

Patients history and physical examinations were considered to be the primary approach of suspecting of developing mucositis, considering the assessment of pain, oral intake amount, secondary infections, bleeding which may be provoked, spontaneous and amount, any infectious symptoms, mucosal integrity, colour of mucosa, lesions. Mucositis the degree of severity is graded by using CTCAE for the National Cancer Institute (version 5) grading adverse events from 1-5 including clinical examination and patients' symptoms. There are other grading systems as well, and they typically evaluate the quantity of lesions, the colour of the mucosa, the presence or absence of bleeding, and the spontaneity of the bleeding similarly (Brown and Gupta, 2020).

Grade which means scoring of recommendation, evaluation, development, and assessment instrument used to assess the evidence of severity and incidence caused by OM, based on the study's design, risk, indirectness, inconsistent reporting, imprecision, and evidence were classified as high, low, moderate, and extremely low (Normando *et al.*, 2017).

Biomarker responsible

Biomarkers can be used to accurately and reliably diagnose, predict, and track the progress of a disease or the response to a therapeutic intervention. They are measurable structures, substances, pathways, or processes that can be secreted by tumors. Patients receiving identical radiation doses are shown to have heterogeneous responses RT in the normal tissues (Normando *et al.*, 2017). Matrix metalloproteinase and pro-inflammatory cytokines are two new classes of biomarkers for mucositis. In an animal model of mucositis, they exhibit increased expression profiles in the digestive tract (Singh, V and Singh, A.K, 2020). A study by Stephen *et al.*, examined the use of CRP and serum ESR as objective indicators of radiation-induced and chemotherapy-induced mucositis in patients undergoing

Table 1: Acc to WHO scale (Kusiak et al., 2020).

Grade 0	No presence of OM found
Grade 1	Redness, inflammation, Irritation of mucosa.
Grade 2	Presence of ulcer, but could eat solids.
Grade 3	Ulcer, implies only diet in liquids (due to mucositis).
Grade 4	Ulcer, nutriment is difficult (due to mucositis).

Table 2: Oral mucositis (Clinical Examinations).

Grade 1	Mucosal erythema.
Grade 2	irregular ulceration or false membranes.
Grade 3	Concurrent bleeding, ulceration, and mild trauma.
Grade 4	Life-threatening outcomes include tissue necrosis, severe spontaneous bleeding.
Grade 5	Loss of life.

radiotherapy and chemotherapy treatment (Normando *et al.*, 2017). The study used the National Cancer Institute of Canada's Common Toxicity Criteria and Head and Neck Radiotherapy Questionnaire to assess acute radiation toxicity.

Radiation-induced mucositis is the most frequent acute toxicity seen in advanced head and neck cancer patients. A biomarker for mucositis could enable objective evaluation of radiation-induced mucosal toxicity, enabling retrospective comparison of treatment side effects. The study aimed to correlate weekly changes in serum ESR and CRP levels with current measures of mucositis in head and neck cancer patients receiving daily radiation therapy or concurrent radiation therapy. Erythrocyte Sedimentation Rate and C-reactive protein measurements were performed using the modified Westergren method and rate nephelometry immunoassay (Mohammed *et al.*, 2011). Gabriela *et al.*, study examined 27 biomarkers, including EGF, CRP, genetic polymorphisms, TNF- α , and ESR. The meta-analysis found that patients with higher chances of developing Oral Mucositis had higher expression of SNPs in the RAD51, XRCC1, and XRCC3 genes. Patients undergoing radiation therapy or chemotherapy were considered according to NCCN guidelines. The eight categories of biomarkers were subdivided into growth factors, acute-phase inflammatory indicators, genetic variables, cytokines, proteins, plasma anti-oxidants, apoptotic proteins, and cells. Growth factors, such as EGF, were found to be the most prevalent, with decreased levels observed during RT treatment and reduced levels in severe patients. TGF-1, another growth factor, was found to be affected by damaged tissues and increased plasma TGF-1 levels in patients with severe radiation exposure.

Cytokines, generated by dying cells or immunological responses, played a role in induced mucositis by attracting inflammatory cells and causing damage. The researchers found that the variation

of cytokines like IL, TNF, and HNC individuals undergoing CRT treatment increased the levels of IL-6 and IL-8. IL-10 levels were found to be high in patients with high-grade mucositis incidence than in low-grade patients. CRP and ESR were the two most frequently present acute inflammatory markers, with fluctuation in ESR levels throughout cancer therapy affecting mucositis classification. CRP is an acute-phase protein and indicator of inflammation, with pro-inflammatory cytokines playing a role in various malignancies. CRP is used to anticipate the risk of patients developing OM in cancer treatment, as it helps neutralize inflammatory compounds and is measured by inflammatory activity (Normando *et al.*, 2017; Ki *et al.*, 2009). Histone protein H2XA is crucial for DNA repair and ability to repair after irradiation, which can be determined by immunofluorescence visualization. The study by Li *et al.*, showed correlations between γ -H2XA and blood having DNA damage mononuclear cells, Peripheral Blood Lymphocytes (PBLs), skin, and human tissues.

The relative fluorescence of γ -H2XA irradiation dosage and PBLs in patients with severe OM and mild OM indicates that it could be useful biomarkers for estimating the role of induction in patients. Circular RNAs (circRNAs) are RNA molecules that structurally form closed loops and exhibit varying degrees of tissue and cell selectivity. CircRNAs are involved in osteoarthritis, heart failure, Alzheimer's disease, cancer, diabetes, therapy resistance, metastasis, stability in body fluids, and specificity diseases. They have been found to be involved in the development of cancer, therapy resistance, metastasis, and stability in fluids from the body (Li *et al.*, 2013). The possibility of circRNAs as disease biomarkers is increased by the discovery of circRNAs from human blood, saliva, and gastric fluids, which can be easily detected in blood samples.

CircRNAs are connected to the growth and development of different cancers, with different expression levels in each case. CircRNA_100290 was discovered to stimulate circRNAs in human Oral Squamous Cell Carcinoma (OSCC) tissues, which reduced CDK6 expression and prevented OSCC cell growth (Zhang *et al.*, 2017). Tissues with LSCC (Laryngeal Squamous Cell Carcinoma) showed differential expression of 698 circRNAs, including up-regulated decreased transcripts of circRNAs. High levels of hsa_circRNA_100855 were associated with advanced clinical stage and lymph node metastases, while low levels were present in LSCC patients with cervical lymph node metastases, inadequate distinction, or a later clinical stage. These studies suggest that circRNAs may be crucial in LSCC development and diagnosis and prognosis (Bahn *et al.*, 2015; Shao *et al.*, 2017).

Prevention Strategies

Preventive and management strategies for Oral Mucositis focus on minimizing its severity and promoting healing through various approaches. One key method is maintaining good oral hygiene through regular brushing, flossing, and the use of

mouth rinses, which has been shown to decrease the progression of mucositis by preventing bacterial buildup and minimizing the risk of secondary infections. Another effective strategy is cryotherapy, where cooling the oral cavity with ice chips during chemotherapy helps to reduce blood flow to the mucosa, thereby lowering drug exposure to the tissues and minimizing damage. Low-Level Laser Therapy (LLLT) is also a potential intervention, as it has been shown to reduce inflammation, alleviate pain, and promote healing by stimulating tissue repair at the cellular level. Additionally, palifermin, a keratinocyte growth factor, has been approved for use in reducing the incidence and severity of mucositis in patients undergoing hematopoietic stem cell transplantation by stimulating the growth and repair of epithelial cells. Together, these strategies offer an integrated approach to preventing and managing oral mucositis, especially in patients undergoing intensive cancer therapies.

Treatment of Oral Mucositis

Several medications have been tried to treat or prevent mucositis, with varying degrees of success.

Cryotherapy

The applying ice chips topically to the oral cavity or mucosal layer while administering chemotherapy reduces the amount of chemotherapeutic drug delivered to the oral mucosa. This impact is probably mediated by a reduction in the flow of blood and local vasoconstriction. According to the guidelines by MASCC/ISOO. It shows that the study explains decreased risk of OM in individuals receiving oral route of cytotoxic agents due to cryotherapy, mainly found useful in chemotherapy and not have applicable part in radiation induced OM (Lalla *et al.*, 2008).

Growth Factors

Palifermin, an IV genetic modification human keratinocyte growth factor-1, is hypothesized to promote the multiplication of epithelial cells, resulting in the expansion of a cell population and restoration to fight OM in patients with blood malignancy (Lalla *et al.*, 2008; Blakaj *et al.*, 2019). The US FDA has also approved palifermin for patients with hematologic malignancies undergoing myelotoxic treatments that call for hematopoietic cell maintenance (Lalla *et al.*, 2008). Moreover, only in the individuals receiving high-dose chemotherapy and entire body radiation therapy for homologized stem cell transplants for hematologic malignancies is it licensed for usage (Blakaj *et al.*, 2019).

Anti-inflammatory agents

NSAIDs medication called benzodamine hydrochloride blocks pro-inflammatory cytokines like TNF- α (Lalla *et al.*, 2008). The U.S. FDA has not approved this drug for this usage, and abundance of the individuals having head and neck cancer receive radiation therapy that is considerably over 50 Gy in addition to concurrent chemotherapy. On the basis of unfavorable findings

from an interim analysis, the most advanced Phase III trial of the medication in radiation-induced mucositis of the oral cavity in individuals along with head and neck cancer had been ended.

Dusquetide is an Innate Defence Regulator (IDR) which binds to the protein p62 and can alter the nonspecific immune response to PAMPs and DAMPs. It was proposed that dusquetide would lessen the immune system's proinflammatory response and signal amplification innate mechanisms, which are thought to be involved in the pathogenesis of OM (Blakaj *et al.*, 2019).

The L-glutamine oral suspension Saforis is a patented product that improves the absorption of the amino acid to epithelial cells. By decreasing the synthesis of cytokines that are proinflammatory and cytokine-related apoptosis, glutamine may lessen mucosal damage and increase the production of fibroblasts and collagen to speed up healing. But according to guidelines of MASCC/ISOO recommended not using due to lack of efficacy.

Antioxidants

Amifostine is thought to act as a scavenger for dangerous ROS, which are investigated to exacerbate mucositis. Amifostine was advised for use in patients with lung carcinoma who were having chemotherapy and radiation to prevent esophagitis, acc to the guideline the use of this medication in Oral Mucositis in radiation or chemotherapy therapy patients could not, however, be recommended by a MASCC/ISOO recommendation due to a lack of sufficient evidence of benefit. N-acetylcysteine, an anti-oxidant, contained in the topical formulation RK-0202 for use in the oral fissure the results of placebo or the inactive drug-controlled trial II it significantly decreased the severity of OM in individuals undergone 50 Gy dose of radiation therapy (Lalla *et al.*, 2008).

Low level laser therapy

Patients with cancer who receive low-level laser therapy benefit from both reduced Oral Mucositis symptoms and prevention of the condition (Algahtani and Khan, 2022). The ROS or anti-inflammatory cytokines have been linked to the aetiology of mucositis, however low-level laser therapy has been proposed to decrease these levels (Lalla *et al.*, 2008). It uses a monochromatic, narrow-band light source for localized treatment (Blakaj *et al.*, 2019). According to some recent research, it can directly activate intracellular chromophores and directly reduce oxidative stress,

Table 3: Oral mucositis (Symptoms).

Grade 1	Few indicators; typical diet.
Grade 2	Symptoms, yet still able to consume and eat a limited diet.
Grade 3	Exhibiting symptoms and impossible to properly eat or drink orally.
Grade 4	Sign that might have deadly repercussions.
Grade 5	Death

which causes a rise in the proliferation of endothelial cells, fibroblasts, pericytes, keratinocytes, and osteoblasts with analgesic effects.²¹ Therefore, the MASCC/ISOO guidelines advocate using LLLT to prevent OM in the context of hematopoietic stem cells behavioral therapy and to prevent the presence of OM in

individuals undergoing HNC without concomitant chemotherapy (Blakaj *et al.*, 2019).

The Quality of Life (QoL) of patients can be improved and hospital stays can be cut down by properly managing oral mucositis. Before initiating chemotherapy and radiation treatment, any

Table 4: Cell-based therapy for mucositis.

Cell-based therapy	Mechanism	Benefits and current research ongoing
Mesenchymal Stem Cells (MSCs).	MSCs can home to damaged tissues, secrete anti-inflammatory cytokines, and promote regeneration of the mucosal lining.	MSCs have shown the potential to reduce inflammation, accelerate tissue repair, and modulate the immune system to decrease the severity of mucositis. Clinical trials are exploring the use of MSCs to treat radiation- and chemotherapy-induced mucositis, showing positive outcomes in tissue regeneration and symptom relief.
Exosomes Derived from MSCs.	Exosomes, which are small vesicles released by MSCs, carry proteins, lipids, and nucleic acids that can mediate repair processes at the cellular level.	Investigations are focusing on the use of MSC-derived exosomes to enhance mucosal healing, offering a targeted, cell-free approach to therapy.
Epithelial Stem Cells.	These stem cells, found in the basal layer of the mucosa, have the ability to differentiate into various cell types required for the regeneration of the mucosal lining.	Epithelial stem cell therapy aims to replenish and repair the damaged mucosal epithelium directly, promoting faster recovery from ulceration and tissue damage.
Hematopoietic Stem Cells (HSCs).	HSCs can regenerate immune cells and influence inflammatory processes during mucositis.	While primarily used in treating hematologic conditions, HSCs are being studied for their ability to modulate immune responses and reduce the inflammatory cascade that leads to mucositis.
Immune Cell Therapies.	Immune-modulating cells, such as regulatory T cells (Tregs) or Myeloid-Derived Suppressor Cells (MDSCs), are being investigated to reduce the excessive immune response that leads to mucositis.	By targeting the immune system's overactivation, these therapies aim to reduce the tissue damage and inflammation associated with mucositis.
Gene Therapy and CRISPR Approaches.	Gene therapy and CRISPR technology are being explored to modify the patient's own cells to resist damage or repair faster when exposed to radiation or chemotherapy.	These therapies could enable cells in the oral mucosa to express protective factors or anti-inflammatory molecules, significantly reducing mucositis severity.
Platelet Lysate (PL) (Sandri <i>et al.</i> , 2011).	PL is emerging as a promising therapy for oral mucositis due to its high concentration of growth factors that promote cell regeneration, reduce inflammation, and accelerate healing.	Studies show that PL can enhance cell proliferation and support mucosal repair, making it effective for patients with oral mucositis from treatments like chemotherapy or graft-versus-host disease. Novel applications, such as <i>in situ</i> gelling sprays with PL, have shown effective mucosal adhesion and sustained growth factor release, facilitating extended therapeutic benefits.

potential causes of mucosal damage should be removed because these treatments may exacerbate and prolong the development of oral mucositis (Kusiak *et al.*, 2020). Pain is the main sign of oral mucositis. The QoL, oral hygiene, and nutritional intake are all greatly impacted by this pain. Therefore, a key element in any mucositis treatment approach is the management of mucositis pain (Lalla *et al.*, 2008). A healthy diet is another factor that could lessen Oral Mucositis symptoms. All products that are acidic, spicy, contain processed sugar, and tobacco and alcohol should be avoided (Kusiak *et al.*, 2020). Utilizing specialized mouthwashes with topical anaesthetic and covering substances, drugs such as antibiotics antifungals, and steroids can help reduce the symptoms of oral mucositis. Sodium bicarbonate or regular saline solutions might ease mild to severe mucositis pain (Brown and Gupta, 2020). Many facilities make use of saline mouthwashes, ice chips, and topical mouthwashes with anaesthetic like 2% viscous lidocaine (Lalla *et al.*, 2008). Vitamin A and E supplements may also be used in the treatment of oral mucositis. Because it is an antioxidant, Vitamin E may lessen the damage caused by oxygen radicals, thereby reducing the severity of mucositis. Additionally, there are various natural ways to treat oral mucositis, such as honey and herbal remedies (Kusiak *et al.*, 2020).

Future therapeutic approaches

The future directions for managing and researching Oral Mucositis are likely to focus on several key areas aimed at improving patient outcomes and understanding the condition more comprehensively.

Personalized Treatment Approaches

Developing individualized treatment plans based on patient-specific factors, such as genetic predispositions, type of cancer, treatment regimen, and baseline oral health. This could lead to more effective and tailored interventions.

Biomarker Development

Continued research into identifying reliable biomarkers, such as pro-inflammatory cytokines and other molecular indicators, that can predict the severity of oral mucositis. This would facilitate early diagnosis and targeted interventions.

Innovative Therapies

Exploring new therapeutic options, including novel topical agents, biologics, and immunomodulatory drugs, to enhance healing and reduce inflammation. Investigations into stem cell therapies and gene therapies may also be promising avenues.

Advanced Oral Care Protocols

Implementing and refining oral care protocols that incorporate evidence-based practices to prevent and manage mucositis effectively. This could include the use of antiseptics, moisturizers, and dietary modifications.

Technological Advancements

Utilizing technology, such as telehealth and mobile applications, to monitor patients' oral health and provide real-time support. Wearable devices might also be developed to assess symptoms and provide feedback on treatment efficacy.

Clinical Trials

Increasing the number of clinical trials focused on oral mucositis to evaluate new treatments and management strategies. Collaborative efforts among researchers, clinicians, and patients can help identify effective interventions.

Education and Awareness

Enhancing education for healthcare providers and patients regarding the importance of oral care and the early signs of mucositis. Increased awareness can lead to better prevention and timely management.

Interdisciplinary Collaboration

Promoting collaboration among oncologists, dentists, nutritionists, and other healthcare providers to create a multidisciplinary approach to managing oral mucositis, recognizing its impact on overall health and treatment outcomes.

Emerging therapies for mucositis

Cell-based therapies, hold significant promise due to their regenerative and immunomodulatory properties. These therapies aim to mitigate mucositis by promoting tissue healing, reducing inflammation, and modulating immune responses. Here are some key cell-based approaches being explored (Table 4) (Bowen and Cross, 2023; Chintha *et al.*, 2021; Yuan and Sonis, 2014).

Cell-based therapy offers advantages such as targeted regeneration, immunomodulation, and minimal side effects. It can repair damaged mucosa at the injury site, regulate immune responses, and reduce inflammation without suppressing immunity. These therapies can improve oral mucositis prevention, diagnosis, and management, ultimately enhancing the quality of life for cancer treatment patients.

CONCLUSION

The systematic review on oral mucositis emphasizes that, although there are several effective strategies for preventing and managing the condition, the diversity of studies, variations in protocols, and individual patient factors necessitate personalized approaches. Potential directions for future research Early identification could be especially important for high-risk patients, optimizing the timing of interventions, and understanding the molecular mechanisms involved in mucosal healing to enhance outcomes for those affected by this debilitating side effect. In summary, oral mucositis is a common side effect of cancer treatment that can significantly diminish quality of life. Various therapies are

available depending on the severity of the condition, including topical and systemic treatments such as corticosteroids, antifungal medications, and antimicrobial mouthwashes, and there are emerging therapies that include cell-based, platelet lysate, immune cells, and many more. Research has been conducted to improve diagnosis and monitoring, with biomarkers like pro-inflammatory cytokines potentially serving to predict the severity of the condition in the future. Finally, grading and classification systems have been developed to assist in assessing and monitoring oral mucositis, ensuring that patients receive the most effective treatments possible.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

OM: Oral Mucositis; **MSCs:** Mesenchymal Stem Cells; **HSCs:** Hematopoietic Stem Cells; **GIT:** Gastrointestinal Tract; **TNF:** Tumor Necrosis Factor; **ROS:** Reactive Oxygen Species; **MTX:** Methotrexate; **CRT:** Chemoradiotherapy; **EGF:** Epidermal Growth Factor; **HNC:** Head and Neck Cancer; **CRP:** C-Reactive Protein; **ESR:** Erythrocyte Sedimentation Rate; **MASCC:** Multinational Association of Supportive Care in Cancer; **ISSO:** International Society of Supportive Oncology; **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats.

SUMMARY

Oral mucositis is a condition characterized by inflammation and ulceration of the oral mucosa, often resulting from chemotherapy or radiation therapy. It can cause mild symptoms like redness and soreness, but can progress to more severe ulcers. Risk factors include chemotherapeutic agents, dosage, and treatment duration. Patient-related factors like age, nutrition, and oral hygiene also affect the severity. Treatment strategies include maintaining oral care, cryotherapy, LLLT, and palifermin. Cell-based therapy, a promising approach, uses stem cells' regenerative and immunomodulatory properties to promote tissue healing and reduce inflammation.

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