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Review Article

ORAL MUCOSITIS INDUCED BY RADIATION/CHEMOTHERAPY; CHALLENGES IN THERAPEUTIC IMPLICATIONS AND FUTURE PROSPECTS

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ABSTRACT

Oral mucositis (OM), which results in mouth ulcers and inflammation, is an unpleasant and frequent side effect of cancer treatments such as chemotherapy and radiation. It has a major effect on patients' quality of life and may even cause cancer treatment to stop. Nowadays, low-level laser therapy, cryotherapy, dental hygiene procedures, and drugs such as palifermin are used as preventative and treatment measures. Risk factors for OM include the type of cancer, the severity of the treatment, and individual characteristics including genetics and dental health. In addition, OM places a significant clinical and financial strain on health-care systems. Even though our understanding and management of OM have advanced, universally effective therapies are still required. Targeting biological pathways, investigating combination treatments, and creating predictive models to evaluate OM are the goals of future research.

Keywords: Mucosal inflammation, Cancer treatment toxicity, Keratinocyte growth factor, Low-level laser therapy, Treatment-related morbidity, Oral epithelial damage.

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INTRODUCTION

Chemotherapy and radiation therapy-induced oral mucositis (OM) is a serious clinical complication which often impacts the quality of life of patients receiving treatment for head and neck cancer. This is an inflammation involving the oral tissues, specifically the mucosa, and is accompanied by ulceration and pain which pose a great challenge in eating, speaking, and general oral hygiene. The condition occurs due to the toxic effects of chemotherapeutic agents on mucosal tissue that result in the disruption of the epithelial barrier. This offense is the dose-limiting toxicity that results in the interruption of cancer treatment or reduction of the intensity of doses that are detrimental to the outcome. Over the recent past, OM has received much attention due to the high prevalence and management or treatment complications among patients as well as health-care givers. The "oral mucositis" describes the inflammation and ulceration of the mucous membrane in the mouth, which frequently happens as a result of chemotherapy and radiation therapy. This is not an infective condition but is secondary to the cytotoxic effects of cancer therapy in damaging the proliferative cells of the oral epithelium. The model of mucositis pathogenesis is described in five phases: initiation, signaling, amplification, ulceration, and healing. The initiation phase includes DNA fragmentation and the generation of free radicals which causes oxidative stress. This is succeeded by the signaling cascades that increase the levels of pro-inflammatory cytokines including the tumor necrosis factor-alpha (TNF-α) and interleukins. The clinically relevant phase of the development of the disease is called ulceration, with the formation of tender stage 3: Open wounds that reveal the surface of the underlying connective tissue. Even though the localized area of damaged epithelium renews itself in due course, the entire process might be delayed, and the healing is further complicated with secondary infection or any other factor that arises due to the treatment [1]. The extent of OM is usually measured using different scales such as the World Health Organization (WHO) scale in which the condition ranges from grade 0 (no mucositis) to grade 4 (moderate-to-severe mucositis requiring parenteral feeding or hospitalization). Others are the National Cancer Institute's common terminology criteria for adverse events (NCI CTCAE) and OM assessment scale (OMAS). Some of these tools assist the health-care providers in evaluating the etendue of the mucosal involvement and the direction of managing the symptoms.

PATHOPHYSIOLOGY OF OM

OM is a complex process that results from the treatment of cancer that mainly includes chemotherapy and radiation therapy affecting the mouth's mucosal barrier physiology. The pathophysiology of OM follows a distinct five-stage process: Starting, increasing, bone, inflammation, formation, and the formation of an ulcer. Each one of them denotes a series of cellular and molecular changes leading to mucosal injury and subsequent healing along with inflammation, oxidative stress, and immune response intervention. Furthermore, OM is not a simple infection as it has severity depending on age, type of therapy, and patient's general health implying that it poses a great challenge to clinicians.

FACTORS INFLUENCING OM SEVERITY

Age, general health condition, and type of cancer treatment are some of the contributing factors to the severity of OM. The incidence of OM in patients receiving chemotherapy is often related with high-dose chemotherapy (HDCT), where the tooth surface could be attacked by therapy targeting rapidly dividing cells in the oral mucosa due to hematologic malignancy. Chemotherapy and radiation therapy also present significant mucosal morbidity, particularly for head and neck cancers; the OM appears to be proportional to the radiation dose and schedule [2].

Other factors which are sources of variability for OM severity include the nutritional status of the patient and genetic makeup. It is well understood that aging patients are more vulnerable to developing deep mucositis due to their age-related changes in the immune system and capacity to restore tissues. Moreover, several studies have shown that poor nutritional status, and especially low nutrient density and low levels of micronutrients including Vitamins C and E have been linked with mucosal vulnerability to injury. Because they have damaged mucosa, patients with dental conditions such dental caries and periodontal diseases that impact the oral mucosa are more likely to develop severe OM [3].

Other factors which are considered to contribute to OM include genetic factors are also known to contribute to the severity of OM. Reduced expression of genes belonging to inflammatory pathways, including TNF-α and interleukin-6 (IL-6), have been found to be associated with an increased risk for severe mucositis. Furthermore, differences in expression patterns of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, implicated in scavenging reactive oxygen species (ROS), can account for the variability of mucositis in patients who receive comparable cancer therapies [4].

PREVALENCE IN PATIENTS UNDERGOING CHEMOTHERAPY AND RADIATION THERAPY

This study also identified OM as being a high-risk complication that affects most patients who undergo cancer treatment, although the prevalence may differ depending on the type of treatment prescribed and the type of cancer. Chemotherapy-induced OM is documented in 20–40% of solid tumor patients receiving conventional chemotherapy, whereas 70–80% of hematopoietic stem cell transplant patients suffer through HDCT for hematologic malignancies such as leukemia or lymphoma [5]. There are evidence showing that OM is more frequent in patients treated with radiation therapy, especially among head and neck cancer patients; the mucosal damage was found more or less in every patient. Radiation-induced OM usually presents in the second or 3rd week of radiotherapy and usually lasts throughout the period of therapy and could last for several weeks after therapy. Fig. 1 illustrates the prevalence of cancer and radiation therapy from 2001 to 2013.

OM is higher in this group because chemotherapy and radiation therapy work on such cells, which are cancer cells but also include the epithelial cells of the oral mucosa. The aggressiveness of the treatment, the length of the course, the particular chemotherapeutic medications utilized, and the patient's pre-existing health of the oral tissues all contribute to the injury of the oral mucosa. For instance, methotrexate, 5-fluorouracil (5-FU), and doxorubicin are some of the agents reported to have severe effects where they cause OM. In the same regard, in radiation therapy, an increase in radiation dose and the combination of radiation with chemotherapy were also identified as factors that increase the risk and severity of OM.

IMPORTANCE OF ADDRESSING OM IN CANCER TREATMENT

OM is a significant challenge in the management of cancer and its treatment since it significantly affects patients' experiences. OM can cause significant illness morbidity such as severe pain, malnutrition, dehydration, and recurrent infections resulting to complications such as sepsis, pneumonia, and bacteremia among others. Furthermore, OM is often interconnected with dose reductions or temporary halts in cancer treatment, which may affect the efficiency of this treatment. Surprisingly, the researchers have found out that disruptions of radiation therapy for head and neck cancers due to OM lead to reduced survival rates [6]

In addition to its clinical effect, OM has a heavy economic cost on health-care systems as postulated by OM. Mucositis in its advanced stage means that the patient needs more intensive support measures, including admissions, IV analgesics, and PN support. This puts pressure on the overall costs of care in terms of monetary value as well as in human economic capital in terms of productivity loss together with lowered quality of life. Furthermore, OM treatment may involve various specialists such as oncologists, dentists, nurses, dietitians, and others to address the focus of symptoms and management to enhance the quality of life and also to prevent complications, as highlighted by Sonis (2020).

Due to the clinical and cost implications of OM, there is now an increasing appreciation of preventive and curative measures. They include cryotherapy, low-level laser therapy (LLLT), topical pain relievers, and drugs such as palifermin a KGF which help to facilitate the proliferation of the epithelial cells and healing. Despite this, the above treatments cannot always be effective, and research on other therapies such as gene therapy as well as molecular therapy is still being conducted. Solving the problem of OM is critical to enhancing the efficacy of cancer treatment and increasing the number of patients' lifespans.

STAGES OF OM DEVELOPMENT: INITIATION, UPREGULATION, SIGNALING, ULCERATION, AND HEALING

OM occurs in a five-phased model which includes the initiation phase. In this stage, the cytotoxic agents including chemotherapeutic drugs and irradiation weaken the basal epithelial cells and their DNA. This results in the formation of ROS that constitute the main factor in mucosal injury. ROS, as well as other free radicals, increase cellular injury through lipid, protein, and nucleic acid oxidation and directly act on the mucosal tissues' cellular equilibrium [7]. The injury to the epithelial cell increases and is accompanied by the firms of the transcription factors including nuclear factor-kappa B (NF-κB), which have a significant role in OM.

The second which is named as upregulation and signaling in OM is also associated with the increased inflammatory processes. Chemotherapy and radiation-induced damage activate NF-κB pathways that trigger the formation of pro-inflammatory cytokines inclusive of TNF-α, IL-1β, and IL-6. These cytokines increase the signaling for inflammation, which prolongs the duration of OM and causes tissue damage to the oral mucosa. However, the breakdown of tissues is accelerated by the activation of matrix metalloproteinases (MMPs), which causes the extracellular matrix to degrade [8].

The third area of OM is identified as the ulceration phase and this is the most clinically painful and disabling of all. In this phase, massive disruption of the continuity of the oral mucosa is seen, which gives rise to the formation of ulcers that penetrate through the entire thickness of the mucosa and involve connective tissue. These ulcers are extremely prone to secondary infection most of which are by bacteria which increase the inflammation and hinder the chances of the ulcer healing. Bacteria also present at the ulcer site could lead to the production of other cytokines that promote inflammation at the site of the ulcer [9]. The obverse and longevity of the ulceration phase depend on the type of cancer treatment being carried out at the same time along with other patient attributes like hygiene and diet if any.

OM in its third phase of the disease is called the healing phase. It starts once the cytotoxic effects of antineoplastic treatment recede so that the inflammation subsides; more epithelial cells proliferate and migrate across the ulcerated areas. That is achieved together with a restoration of the extracellular matrix together with the clearance, were existent, of bacterial infections. The duration for the healing phase of mucosal injury also depends on the degrees of initial mucosal injury and in excess of complications such as infection or continued therapy. Occasionally, treatment is only "partial" and can result in long-term pain or persistent mucosal lesions [10] (Table 1).

ROLE OF INFLAMMATION AND IMMUNE RESPONSES

Inflammation is central to the process of odontogenic cysts, especially during the upregulation and ulceration phases of OM. TNF-α, IL-1β, and IL-6 being epi-dermal action cytokines promote the inflammatory response in the oral mucosa. These cytokines function as chemoattractants that control the migration of immune cells such as neutrophils and macrophages to the mucus membranes. After becoming recruited, these immune cells release further inflammatory mediators and ROS and are involved in further tissue damage and sustaining inflammation [10]. Although previously perceived as a defense mechanism needed to clear infection, the immune process can actually amplify tissue damage, thus developing a cycle of inflammation and damaged tissue.

Consequently, the involvement of the immune system in OM is made complicated by the bacterial colonization that occurs during the ulceration phase. Invasion of ulcerated tissue by the bacteria elicits an

inflammatory response which manifests in cytokine and ROS efflux and thereby contributes to tissue injury. This immune response may well be the reason why OM tends to be chronic in patients who are on long-term cancer treatments because the presence of bacterial infections through severe delays the healing process [11].

CELLULAR MECHANISMS AND THE ROLE OF ROS

In light of the cellular response, ROS is known to be implicated to OM pathogenesis. ROS are highly reactive molecules which are produced in response to chemotherapeutic and radiation treatments of cancer due to destruction of the mitochondrial respiratory chain and other cellular organelles. ROS induces lipid, protein, and DNA peroxidation of cellular structures, disrupts cellular functionality, and prompts programmed cell death [12]. This oxidative stress is one of the major ways through which cancer treatments promote mucosal damage.

Besides directly attacking cells, oxidative stress also leads to the activation of NF-κB, and p53 signaling pathways, which again are vital to inflammation in OM. These signaling pathways modulate the production of pro-inflammatory cytokines that enhance the local inflammatory response and increase tissue damage. Oxidative stress is known to be persistent during cancer therapy, and this means that inflammation does not resolve at the appropriate time, this leads to prolongation of the ulceration phase, and mucosal healing [13].

RISK FACTORS AND PREDICTORS OF OM

Chemotherapy and radiation therapy are common cancer treatment modalities that are well known to cause OM with many predisposing factors. Thus, it is imperative to identify how different types of therapies, the cancer type, dosage, and the duration of the treatment will predispose a patient to the development of OM and the severity of the disease. Furthermore, factors that are specific to the individual patient including the genetic factors, hygiene practices as well as the nutritional status of the patient will also affect the risk of OM. These various factors make it rather difficult to forecast the occurrence and intensity of OM, yet it is imperative to enhance effective organizational processes relating to the treatment of cancers and the handling of patients.

CHEMOTHERAPY-INDUCED VERSUS RADIATION-INDUCED OM

Chemotherapy and radiation therapy are both known to cause OM, but they do so by inflicting different levels of mucosal injury, which in turn provides a basis of the differences in symptomology and severity of the resultant condition. This kind of OM results from the systemic effects of cytotoxic chemicals used to treat various diseases, which also impact other tissues, including the oral cavity's lining epithelial tissues, in the process of combating the targeted diseases. It thus results to a widespread epithelial injury together with an impaired mucosal barrier. Among them, methotrexate, 5-FU, and doxorubicin are most likely to induce OM [14]. Om involves apprehended chemotherapeutic agents and their dosages followed closely by the dangers and degree of seriousness projected to chemotherapy patients.

On the other hand, radiation-induced OM is characterized by lesions that are associated with radiation injury of the localized head and neck tissue due to radiation treatment of malignancy. Radiation-induced OM is usually more profound than chemotherapy-induced OM since radiation influences the tissues within the field of irradiation which entails the oral mucosa. In these patients, the rate of OM is almost 100%, and the majority of patients experience severe ulceration at the end of the treatment [15]. The severity of radiation-induced OM is also cumulative in nature that means that the extent of tissue damage increases with successive treatment, and the patient discomfort is also subsequently enhanced.

One of the factors which differentiate chemotherapy-induced and radiation-induced OM is the onset of the symptoms. It is noteworthy that patients receiving chemotherapy are most likely to develop on nodular after 7–10 days following the onset of antimarketing agents while patients receiving radiation therapy usually become predisposition to ON by 2–3 weeks after beginning radiation treatment. Furthermore, although the causes of OM due to chemotherapy may recover quite soon after the cessation of the therapy, radiation-induced OM may take several weeks or even months to heal depending on the extent of mucosal damage and the ability to heal of the patient [16]. Table 2 states various factors and their chemotherapy and radiation-induced OM.

ROLE OF CANCER TYPE, DOSAGE, AND THERAPY DURATION

From the evidence it is established that the specific type of cancer being treated is determinative of the level of risk and severity of OM. Patients with head and neck cancers, especially those who have been administered radiation therapy, are most vulnerable to the severe outcomes of OM. In doing so, it can be fairly stated that the radiation field frequently includes the covering of the oral cavity making the mucosa directly susceptible to ionizing radiation injury. In the same manner, patients receiving HDCT for hematologic malignancies including leukemia or lymphoma are also at a comparatively higher risk because of the intensity of the chemotherapy they undergo [16]. In these cases, OM can result in severe mucositis which can limit the dose intensity of chemotherapy; that is, treatment may have to be reduced or stopped to avoid exacerbating the side effect, which in turn, can compromise cancer therapy.

It is clearly understood that the dosage of cancer treatment has a major influence on the progression of OM. Chemotherapy and radiation therapy that are administered in large volumes and dosages are also known to increase the probability of mucositis. For instance, patients taking high dosages of methotrexate or 5-FU are way much more vulnerable to OM than patients who are on low doses of the same substances [17]. In radiation therapy, the total dose of radiation, the fractionation schedule, and the volume of the tissue receiving radiation are some of the factors that have an influence on the severity of OM. Fractional irradiation therapy which consists of delivering low-dose radiation in larger intervals is often used to mitigate the effects of OM; nonetheless, the effects of total radiation dosage in such instances lead to severe mucosal injury.

It is also important to note the length of time the patient has been undergoing therapy since it is also a key factor that contributes to the development of OM. Chemotherapy cycles that last for a very long period, or radiation treatment lasting for a long period also may enhance mucosal damage since the tissues will be under the influence of the cytotoxic agents or even the effects of radiation for a long time. Where both chemotherapy and radiation therapy are used at the same time (chemoradiation), the risk of OM is even higher because the combined toxicities of the two treatments lead to an even higher degree of damage to the oral mucosa [18].

PATIENT-RELATED FACTORS (GENETICS, ORAL HYGIENE, AND NUTRITION)

There are several patient-related factors which can also be viewed as affecting OM risk and severity: These are related to treatment as well as patient profiles. In regard to patients, one of the important factors is the role of genetics. Several potential biomarkers have been studied including genetic polymorphisms in genes involved in inflammation, DNA repair, and oxidative stress which may contribute toward the development of severe OM in certain individuals. For instance, the polymorphisms of the genes encoding pro-inflammatory cytokines including TNF-α and IL-6 have been reported to be risk factors for OM, since people harboring such genetic variants tend to experience increased inflammation in the oral mucosa [19]. Likewise, genetic variations that determine the metabolism of certain chemotherapeutic drugs, for instance, methotrexate affect the predisposition to develop OM since alterations in drug metabolism may lead to a higher accumulation of toxic levels of drugs in the oral epithelium.

Another important determinant of OM is the oral hygiene status of a patient. Children with "poor oral health habits and those children with a previous history of some systemic diseases or local pathological conditions of the mouth including periodontal disease or dental caries are at increased risk for the development of severe OM. This is because if an individual has oral infections or inflammation, then the cancer therapeutic interventions will increase the damage to the mucosa. Therefore, it is imperative to practice good oral hygiene before and during cancer therapy to minimize OM. This may include dental checkups, scaling and polishing, or even the use of antiseptic mouthwash age to lower bacterial count in the oral cavity [19].

This paper also includes nutrition as one of the most important factors that contribute toward OM. Patients with various nutrient deficiencies, especially Vitamin C, Vitamin E, and Zinc, are also at a higher risk of acquiring OM than healthy patients. Flavonoids are known to act as antioxidants and possess anti-inflammatory properties which help to support the oral mucosa lining, regulate the immune system, and enhance tissue repair mechanisms. Consequently, one may be severely affected by mucosal injury if the person is a cancer patient who is malnourished or cannot feed on balanced foods. Patients who are deemed to be at risk of OM may require enteral feedings in the form of oral supplements or PN [20].

CLINICAL MANIFESTATIONS AND DIAGNOSIS OF OM

OM is a clinical manifestation that has an array of clinical symptoms that change in Clinical Severity, and complications often cause significant distress to various cancer patients. This condition may have a certain impact on patient's quality of life because they can have pains, malnutrition, and an increased risk of secondary infections. Knowledge of the grading systems of OM becomes important while determining the severity of the condition and which treatment measures to be applied.

SYMPTOMS AND PROGRESSION OF OM

OM often starts with inflammation of the oral mucosa, which in the initial state is characterized by such signs as erythema and soreness. These symptoms normally manifest within 7–10 days of onset of chemotherapy or 2–3 weeks of radiation therapy [20]. It is as the disease advances that the lesions develop on mucosal surfaces and become painful ulcers, commonly at the buccal mucosa, tongue, soft palate, and the floor of the mouth. The lesions can be presented in a variety of sizes, which are usually accompanied by a halo of inflammation that causes pain to the patient.

In the worst-case scenarios, these patch-like ulcers amalgamate and occupy a wide area of the oral cavity causing severe pain, and speaking, eating, and even drinking becomes a great challenge. Such symptoms as dysgeusia, xerostomia, and problems with swallowing can be witnessed as a result of OM apart from the physical discomfort it brings [21]. The ulcers may also become secondarily infected either by oral bacteria such as streptococcus or fungal infection such as candida albi cans which further complicates the patient's condition and delays his/her recovery. If left untreated, OM can persist for weeks; and in cases of patients receiving long-term or high-dose anti-cancer therapies.

The progression of OM is typically described in terms of its five stages: start, enhance, activation, lesion formation, and tissue repair. The initiation phase is characterized by DNA damage and during the promotion phase there is the onset of inflammatory pathways and signaling cascades that lead to disruption of the mucosal barrier. The most critical phase of the illness is the ulceration phase where the patients are most uncomfortable, and there is a predisposing factor to infection. The last stage is the healing stage and during this stage, the damaged mucosa starts repairing itself but this process may take a long time and will be further slowed down by continuing cancer treatments.

DIAGNOSIS AND GRADING SYSTEMS

OM can only be diagnosed clinically by recognizing certain clinical features such as erythema and mucosal ulceration together with pain. Nevertheless, due to the nature of the condition being variable in each case, reference systems that provide the gradation of OM should be used to provide cookies and serial reports of the condition.

For this purpose, several grading scales have been designed which enable the evaluator to assess the performance of the learner at a given time. Classification of oral toxicity is done using a number of scales, one of the most widely used is the WHO Oral Toxicity Scale. This scale evaluates mucositis on a grading system ranging from 0 to 4, where grade 0 indicates the absence of mucositis, while grade 4 signifies severe mucositis that inhibits oral intake, including fluids (WHO, 2017). Learned use scale is popular also because it permits to arrangement of patients into groups quickly and satisfies the requirement of the scale used in clinical trials and practical work.

Another globally known system is the NCI-CTCAE which also grades OM from grade 0 to 4. This system gives more focus to the functional effect of OM most, especially the effects on the ability of the patient to swallow and take foods and liquids. The OMAS is actually even more precise, as it measures both, erythema and ulceration, in various regions of the mouth [22]. OMAS depicts the severity of mucositis from a scale of no mucositis 0 up to severe ulceration 5, this tool is also, especially favorable for research studies as it provides a fine gradation of the disease's progression.

MANAGEMENT AND TREATMENT OPTIONS FOR OM

The approach to the treatment of OM consists of the prevention of development and the mitigation of signs of OM in the course of cancer treatment to maximize patient's quality of life. OM can make patients suffer from severe pain, have a problem with nourishment intake, and can lead to increased susceptibility to infections; thus, effective and timely treatment is required. Preventative measures, medicinal treatment, and other upcoming forms of therapies have been formulated to combat OM.

PREVENTIVE STRATEGIES

Oral hygiene protocols

One of the important preventive measures against OM is effective oral hygiene. Hygiene care for the oral cavity reduces bacterial adherence and subsequent infection that provides additive injury to the mucosa by chemotherapy/radiation treatment. Measures practiced are the use of a soft-stiff bristle toothbrush, fluoride-containing pastes, and mouthwashes excluding alcohol. It is also advised that cancer patients going for treatments stay away from liquids such as alcohol, cigarettes, and products that have acidic or spicy tastes as they exacerbate the condition of the oral mucosa [23]. Dental examinations and the treatment of the existing oral condition including periodontal diseases or dental cavities are advised before the commencement of the cancer treatments. This in a way is helpful so that likely sources of infection are kept away or reduced so that OM may not develop or even if it has developed, worsen. Measures of oral hygiene have been proven to decrease the risk of developing severe OM and to preserve the oral mucosa barrier while undergoing cancer treatment [24].

Cryotherapy and LLLT

Some of the interventions that have been used include cryotherapy, where the patient has ice chips or cold water to cool the oral cavity during chemotherapy; this has been noted to prevent OM, especially for patients receiving agents like 5-FU. Cryotherapy has a cooling impact that leads to vasoconstriction within the oral mucosa thus restricting the delivery of cytotoxic compounds to the oral tissues as well as minimizing mucosal injury [25]. Another preventive approach that has been discussed in the recent past is the LLLT. The treatments using LLLT refer to the application of low-power lasers that aim to spur the body tissues' natural cell repair abilities and lessen inflammation. Its efficacy to prevent and treat OM has been well-documented including in patients that are receiving radiation therapy for head and neck malignancies. LLLT also contributes to cell cycle regulation, variation in oxidative

stress and inflammation, and also accelerates wound healing [26]. It has been found that LLLT can help to lessen the probability and extent of OM and can also minimize the recovery time required for children who already suffer from OM.

Pharmacological prevention (keratinocyte growth factor, palifermin)

To decrease the incidence of OM in patients under HDCT or radiation therapy, several pharmacological agents such as KGF and palifermin have been invented. Palifermin is a recombinant human KGF that promotes the growth and development of epithelial cells and accelerates the healing process of the injured mucosa. They include OM prevention in patients with hematological malignancies who are candidates for stem cell transplantation or receiving HDCT and/or radiation [27]. Palifermin has the capacity to decrease the occurrence and intensity of OM because it promotes the proliferation of mucosal epithelial cells and thus gives protection against cytotoxic compounds. According to various research, palifermin has the potential to shorten the length of stay of severe OM and enhance the potential of patient's recovery by continuing cancer therapy without interruption and with minimal dose modification.

SYMPTOM MANAGEMENT

Pain relief options (topical anesthetics and analgesics)

In OM treatment, the administration of analgesics is an important issue because mainly the ulcerative lesions related to the disease are in sharp pain. Topical astringents such as lidocaine or benzocaine are applied to the sensitive regions to gain a kind of anesthesia of the areas for a limited amount of time. It is possible to use these agents with direct administration on the ulcers in the form of gels, sprays, or mouthwashes [28].

Moderate-to-severe pain may require the use of systemic analgesics, normally these are not recommended for long-term pain relief. More severe pain is usually treated using non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. However, the use of opioids must be controlled because of side effects and also because they are habit-forming. It is common that the treatment plans are personalized according to the severity of OM and the patient's general health as well as tolerance to pain [29].

Nutritional support and oral care

That is why, because of the pain and dysphagia that companion OM, adequate nutrition support is critical for the medical treatment of the patient with cancer. Inflammation of the mucosal lesions should be treated by prescribing the patient a soft or even liquid diet. Pan Feeding Tubes may be needed in some severe cases to provide adequate intakes of foods and nutrients. For further, nutritional supplements and meal replacements may also assist in avoiding malnutrition and weight loss in patients suffering from OM [30].

Along with nutritional interventions, oral care has to be maintained day in and day out to counteract infection and treat symptoms. These measures involve proper utilization of oral rinses, especially saline and bicarbonate solutions which help in soothing the mucosa and cleaning debris. Other measures which can be applied to control or prevent secondary infections include rinses such as chlorhexidine although with should observe the frequency of such rinses in order not to worsen the irritation of the mucosal tissues.

EMERGING TREATMENTS

Gene therapy and targeted molecular treatments

New treatments for OM are now being developed, including gene therapy and molecular medicines that target the fundamental causes of the disorder. Gene therapy targets the genes that are involved in inflammation, tissue repair, and oxidative stress. Through such pathways, gene therapy may help in minimizing the intensity of OM and aid in the fast-healing process. Further studies are still being conducted to establish the unique genes and molecules which can be regulated to remove the chances of OM in cancer patients [31]. Another approach of interest involving gene-editing tools is the approach that focuses on targeting the expression of pro-inflammatory molecules including TNF-α and IL-6 which are biomarkers in OM development. Probably by decreasing the concentrations of these cytokines, gene therapy shall possibly lower inflammation and therefore prevent damage to the mucosa. These therapies are still in the experimental phase and there is a need for more constructive clinical trials to establish their safety and effectiveness.

New pharmacological interventions under research

Several new pharmacological interventions are currently under investigation for the treatment of OM. These include agents that target specific molecular pathways involved in mucosal injury and inflammation. For example, inhibitors of NF-κB, a transcription factor that regulates the expression of pro-inflammatory genes, are being studied as potential treatments for OM [16]. By blocking the activation of NF-κB, these inhibitors may reduce the inflammatory response and prevent the progression of OM.

Other agents, such as antioxidants and anti-inflammatory drugs, are also being tested for their ability to reduce oxidative stress and inflammation in the oral mucosa. For instance, curcumin, a natural anti-inflammatory compound, has shown promise in reducing the severity of OM in preclinical studies. Clinical trials are ongoing to determine whether these compounds can be used as effective treatments for OM in cancer patients [18].

IMPACT OF OM ON CANCER THERAPY OUTCOMES

OM is a major and dose-limiting toxicity of chemotherapy and radiotherapy for cancer, which largely affects cancer treatment. The condition results in poor compliance to treatment regimens, reduced dosages, and extra health expenses which are detrimental to cancer patients' outcomes. In addition to interfering with cancer-receiving therapy time, OM also increases patients' physical, emotional, and financial challenges as well as the burden on the health-care system. It is effective to learn more about the role of OM in cancer treatment not only in enhancing the care quality of patients but also in developing a systematic approach to the treatment.

DELAYS IN TREATMENT DUE TO OM

Perhaps the most severe and undeniable effect of OM is the time it prolongs a patient to begin treatment for cancer. Chemotherapy and radiation therapy have a timetable and dosage-dependent treatment plans with the aim of having optimum effect. However, the exacerbation of OM requires the cessation of therapy to help the mucosal repair itself. These delays are even more awful for patients receiving radiation therapy for head and neck cancers. More research has revealed that for every day of delay in radiation therapy, there is a 1% reduction in the probability of achieving local tumor control [1]. Hence, even if the treatment is interrupted due to OM for any short time, there are high risks of failure to cure the illness. Fig. 2 illustrates the delay in the treatment procedure for OM.

In the same way, chemotherapy itself entails the steady use of cytotoxic drugs with the purpose of killing rapidly proliferating cancer cells. When OM comes the way of patients, they might have to delay their chemotherapy sessions. This has a demoralizing effect on the cancer cells, enabling them to bounce back in case they want to increase in number. This may decrease effectiveness of the treatment process and it may lead to development of poor outcomes of the disease. Patients bearing hematologic malignancies appear to be at risk of such delays because their treatment needs often involve extensive dose-intense chemotherapy that is highly sensitive to disruption by OM [32].

REDUCED DOSAGE INTENSITY AND ITS EFFECT ON OVERALL PROGNOSIS

Apart from early treatment and diagnosis, OM more often results in a reduction in chemotherapy and radiation dose. The soreness and

Table 1: Stages of oral mucositis and key biological processes

Stage	Key biological processes
Initiation	DNA damage, ROS generation, oxidative stress, activation of NF-κB
Upregulation	Production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), activation of MMPs
Signaling	Amplification of inflammatory pathways, degradation of extracellular matrix
Ulceration	Breakdown of mucosal lining, formation of ulcers, bacterial colonization
Healing	Resolution of inflammation, epithelial regeneration, re-establishment of mucosal integrity

TNF-α: Tumor necrosis factor-alpha, IL-1β: Interleukin-1β, IL-6: Interleukin-6, ROS: Reactive oxygen species, NF-κB: Nuclear factor-kappa B, MMPs: Matrix metalloproteinases

Table 2: Comparison of chemotherapy-induced and radiation-induced oral Mucositis

Factor	Chemotherapy-induced OM	Radiation-induced OM
Mechanism of damage	Systemic cytotoxic effects on rapidly dividing cells	Localized damage due to ionizing radiation
Timing of onset	7–10 days after chemotherapy initiation	2–3 weeks after the start of radiation therapy
Incidence	20–40% of patients receiving conventional chemotherapy	Up to 100% of head and neck cancer patients receive radiation
Duration	Resolves relatively quickly after therapy cessation	May persist for weeks or months post-therapy
Severity	Dependent on the chemotherapeutic agent and dose	Cumulative and worsens with each successive treatment

OM: Oral mucositis

Table 3: Oral mucositis grading scales and their criteria

Grading scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO oral toxicity scale	No mucositis	Soreness/erythema	Ulcers can eat solids	Ulcers require a liquid diet	Severe mucositis, alimentation not possible
NCI CTCAE	No mucositis	Asymptomatic or mild symptoms	Symptomatic can eat a soft diet	Symptomatic, cannot swallow solids	Life-threatening, requires intervention
OMAS	No erythema/ ulcers	Mild erythema/1 small ulcer	Moderate erythema/ multiple small ulcers	Severe erythema/ large ulcers	Ulcers covering large areas of the oral mucosa

WHO: World health organization, NCI-CTCAE: National cancer institute's common terminology criteria for adverse Events, OMAS: Oral mucositis assessment Scale

Table 4: Summary of oral mucositis treatment approaches and their efficacy

Treatment approach	Mechanism of action	Efficacy	Limitations
Oral hygiene protocols	Reduces bacterial load and prevents secondary infection	Effective in reducing mild-to-moderate OM	Limited efficacy in severe cases
Cryotherapy	Reduces blood flow to oral mucosa	Effective in preventing chemotherapy-induced OM	Limited to certain chemotherapy agents like 5-FU
Low-level laser therapy (LLLT)	Promotes healing and reduces inflammation	Proven to reduce the severity and duration of OM	Requires specialized equipment and trained personnel
Pharmacological (Palifermin)	Stimulates epithelial cell growth	Reduces incidence and severity of OM in high-dose chemotherapy	Expensive and limited to specific cancer treatments
Analgesics and topical anesthetics	Provides pain relief and symptom management	Effective in managing pain associated with OM	Does not address underlying cause of OM

OA: Oral mucositis

individuals feeling pain and discomfort during OM, in combination with the possibility of a secondary infection, make oncologists have to reduce the aggressiveness of therapy. Despite the seeming effectiveness of this approach in treating the initial signs of OM, it would have adverse effects on outcomes of cancer.

Low dosage density may compromise the general efficacy of Cancer treatment. First, both chemotherapy and radiation therapy are delivered to the maximum dose tolerance because every attempt is made to eliminate as many cancer cells as possible. Reducing the dose detracts from the treatment's effectiveness in eradicating cancer cells, which leads to the development or reemergence of the disease. This is especially worrisome for rapidly growing cancers that require a high-dose course of treatment to effectively eliminate cancer cells and prevent recurrence [33].

Unfortunately for patients with head and neck cancers, the effect of dosage intensity in relation to treatment outcomes is quite clear. Patients who are in OM treatment have reduced doses of radiation tend to exhibit higher local recurrence rates and lower survival rates than those who can receive full planned radiation treatment [33]. For example, in patients with solid tumors or with hematologic malignancies receiving chemotherapy, lower dose intensity has been linked to worse overall survival and significantly inferior PFS [34]. Table 4 summarizes the treatment approach and its efficacy on oral mucositis.

CURRENT CHALLENGES AND FUTURE DIRECTIONS IN OM RESEARCH

OM is still a clinical problem in oncology irrespective of the recent progress in cancer treatment and symptom management. As previously indicated, OM is multifactorial and consequently, managing it has been discovered to be challenging; the numerous methods that can be adopted are however not as effective across the board. The current status of existing treatments, the increasing need to shift from conventional treatments, and biomarkers and predicted models' liberalization are the main areas of further research.

IMPORTANCE OF COMPREHENSIVE OM MANAGEMENT IN IMPROVING PATIENT OUTCOMES

Therefore, it is important that OM should be approached from a complete Perspective to enhance the overall prognosis of patients with cancer. OM can result in long periods between the diagnosis and the initiation of treatment, as well as, in reduction of cancer treatment dosage which minimizes its effectiveness. In radiation therapy, especially in H&N cancer patients, minor delays in treatments affect local tumor control probability while in chemotherapy, patients can develop increased uncontrolled cancer cell growths if doses are cut back to let cancer cells multiply at high rates thus low chances of remission or cure.

Thus, the integrated approach to OM requires the use of both preventive measures and efficient management of symptoms allowing the patient to carry on with the cancer treatment without extensive breaks. The preventive measures may include the implementation of oral hygiene measures, cryotherapy, usage of LLLT, or pharmacological management of a patient to reduce the occurrence of OM or to lessen the intensity of the symptoms. Furthermore, in a care plan for the management of OM, the caregivers should ensure that the child has adequate food to avoid malnutrition and also ensure proper dental hygiene to avoid secondary infections. What remains, therefore, is the coordination of these various treatment approaches to minimize the overall impact of oral mucositis on the patient's cancer treatment while ensuring effective delivery of therapy [35].

The application of personalized medicine concepts also could be a promising direction in OM management enhancement. Since there are variations in patient outcomes for cancer therapy and OM treatment, focused care plans that address genetic makeup, the use of specific protocols for treatment, and other patient risk factors may prove cost-effective and efficacious in the control and treatment of OM. For instance, patients with genetic risk factors for the development of severe OM could be provided with high intensity of intervention including early initiation of LLLT or administration of Palifermin to minimize the occurrence of severe mucositis. They could enhance patient position by making less occurrence and intensity of OM and further enabling the delivery of cancer therapies more steadily.

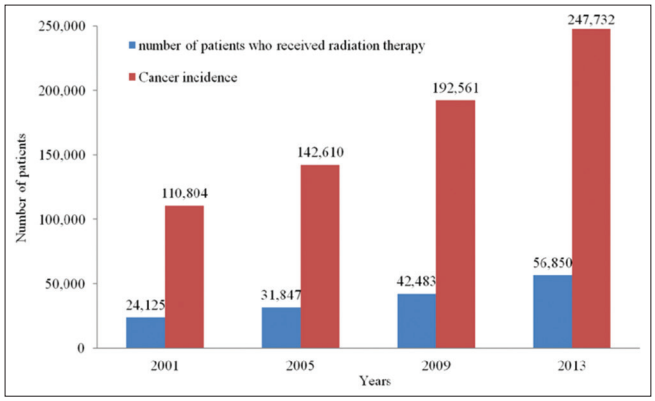

Fig. 1: Trends in cancer incidence and radiation therapy utilization (2001–2013)

POTENTIAL FOR FUTURE ADVANCEMENTS IN OM PREVENTION AND TREATMENT

Improvement of OM prevention and treatment in the future provides a better chance of enhancing the level of patient care. Current research seeks to determine biomarkers and make a predictive model of OM; this means clinicians will have a chance of identifying patients at risk even before they develop the symptoms. Hypotheses that genetic, clinical, and treatment factors, might be incorporated to identify the potential candidates for preventive intervention with LLLT or pharmacologic agents. Such an approach would allow treating OM in every patient, as a clinician, individually depending on the patient's risk factor profile, which would increase the efficiency of preventing and treating OM.

Besides the predictive models, the development of novel pharmacological agents in OM is expected to produce further treatment. As current treatment options for OM are modestly effective and the risk-benefit ratio often unfavorable, there are targeted therapies that target the molecular pathology of OM, for example; inhibitors of NF-κB and antioxidants which lessen oxidative stress are currently being explored as better interventions for OM prevention and treatment. Other currents in OM treatment may also be provided by new gene therapies as well as regenerative medicine for modulation of mucosal healing and inflammatory reaction.

Other technologies that might be incorporated into future OM management include stem cell usage and tissue engineering. These therapies have the intention of fastening the healing of the lesion and the recuperative process to regain the integrity of the oral mucosa thus minimizing the days and intensity of OM. Incorporation of the new therapies outlined in the research into the practice could lead to improvement in the quality of care offered to the OM patients, thus leading to enhanced quality of life.

Thus, it can be stated that, though the current treatment of OM is to some extent effective, OM remains an essential problem among cancer patients and clinicians. Further advancements in techniques which are more efficient, more accessible, and less generalized for OM are crucial in mitigating the effects of the condition on cancer management. This will help health-care providers to manage the current concerns and adapt to future versatility in OM that would help enhance patients' quality of life while likes by minimizing the impacts of OM on cancer care.

The article under discussion is a comprehensive review of OM, which is among the most prevalent and serious complications of cancer therapy, primarily chemotherapy and radiation therapy. This review encompasses

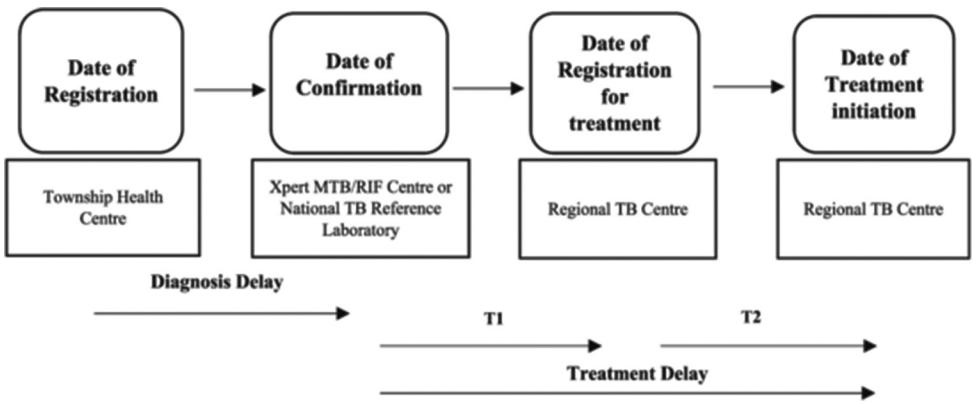

Fig. 2: Impact of oral mucositis on cancer treatment efficacy and timely therapy completion

pathophysiology, risk factors, clinical manifestations, diagnosis, management, and impact of OM on cancer therapy outcomes [36].

CONCLUSION

OM preventive measures, patient care, and emerging curing protocols used by the management are aimed at preventing or reducing the damage of oral mucosa and enhancing patients' survival. It also examines the ways of preventing OM including practicing good oral hygiene, going for cryotherapy, and taking certain pharmacological agents such as palifermin. The adjunctive interventions, specifically, focus on the improvement of the patient's symptoms, such as pain control and nutrition, in the course of cancer treatment. Essential treatment factors that were identified include total dose, daily fractionated dose, and pre-treatment worst baseline OM whereas patient-specific factors included age, gender, prior viral or bacterial infection, concurrent infection, serum IL-6 level, lactobacillus strain, oral decontamination regimen, fractionated radiation dose, type of antifungal treatment and total radiation dose. Nevertheless, it is perpetual to put emphasis on chemo- and radiation therapy as the main causes of mucosal injury, provided that the type of cancer, dosage, and duration of therapy all contribute significantly to the degree of OM. Other factors that influence the probability of OM are also adduced from the patient's side, among them being genetic predisposition, oral hygiene, and nutritional status. Recognizing these risk factors and predictors is crucial, especially in designing individualized intervention plans that would reduce the odds of OM and enhance the clinical outcomes of patients with cancer during their treatment. More current therapies that are still under exploration include gene therapy and targeted molecular therapy as these may offer better treatment solutions for OM that are more patient-specific. It results in delays in cancer therapy, a decrease in dosage intensity, and increased health-care costs among patients with OM. These consequences are capable of affecting the effectiveness of cancer treatment, specifically among patients with malignant forms of cancer, which entail the application of high-dose regimens. Moreover, there are substantial cost implications of OM to the financial resources of health-care facilities in particular and health-care systems in general. Accordingly, as OM forms a major area of morbidity for cancer patients, efforts should be directed at the development of preventive and therapeutic preventive measures to improve the outcomes of the patients and decrease the overall costs of cancer treatment.

Expert opinion

The authors provided a good structured overview of the more complex pathophysiology of OM as a five-stage process involving initiation, upregulation, signaling, ulceration, and healing. This model thus gave an easily understandable framework for the development of OM, both cellular and molecular changes. Strikingly important in the discussion are the roles of ROS and pro-inflammatory cytokines in the pathogenesis of OM, which fit with the present scientific understanding. The discussion of risk factors for OM is well-rounded in that it encompasses not only treatment-related factors such as type of cancer, dosage, and duration of therapy but also patient-related factors, including genetics, oral hygiene, and nutrition. Understanding these multifactorial influences is necessary to better develop prevention and management strategies. The description of the clinical manifestations and diagnosis of OM is very detailed and practical from the authors. In addition, the inclusion of multiple grades (WHO, NCI-CTCAE, and OMAS) of the disease is beneficial in aiding clinicians in describing the severity of OM and monitoring treatment response. Such standardization is critical for both clinical and research applications. The review of management and treatment options is so vast and updated that it covers a range of approaches, including preventive strategies such as oral hygiene protocols and cryotherapy, new approaches such as LLLT, and targeted molecular therapies. This balance between established and experimental treatments brings about a more thorough view of OM management. This is one of the strengths of the review: It actually places much focus on the impact of OM on the outcomes of cancer therapy. Through this, the authors highlight just how OM may lead to delays in treatment and reduced dosage intensity, thereby jeopardizing the outcome. It is rather a forward-thinking discussion on current challenges and future directions in research concerning OM, identifying key areas where a bit of improvement should be made. Correctly, the authors call for personalized medicine approaches and the power of biomarkers and predictive models in managing OM. The authors might have used a deeper analysis of the current evidence for multiple treatment modalities in this review. Further scientific strength would be added to the article if a better discussion about the weakness of the studies and why large-scale, well-designed, randomized controlled trials are needed were provided. In addition, though the review does mention some of the economic aspects related to OM, a more intensive cost-benefit analysis of different prevention and treatment methods would be helpful for any health-care-related decision-makers. This review article provides an integrative summary of OM as a complication of chemotherapy and/or radiation therapy that is scientifically sound. This manuscript effectively synthesizes the current knowledge in pathophysiology, risk factors, clinical aspects, and management of OM, while still pointing out the areas in need for further research. The resource will be valuable to practicing clinicians, researchers, and others in cancer care that desire insights into both clinical practice and future investigations of OM.

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AUTHOR'S CONTRIBUTIONS

Pradeep JS: Literature review, Data curation, Writing-original draft, and Evaluation; Jey Kumar Pachiyappan: Literature review, Data curation, and Writing-original draft; Jagan Senthil Kumar: Writing-original draft, Conceptualization, and Critical Evaluation; Roshan Tej Sekar: Writing-original draft, Conceptualization, and Critical Evaluation; Kousalya Selvaraj: Review and editing, Supervision, Evaluation, and Visualization.

CONFLICTS OF INTEREST

The authors declared no conflict of interest.

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