

Review Article

Management of Chemotherapy induced Mucositis

Abstract:

Oral mucositis is a severe ailment that causes erythema, edoema, and ulceration of the oral mucosa, as well as pain and oral intake restrictions. Chemotherapy and radiation therapy are the most often utilised cancer treatment options. Despite the fact that these treatments are used to improve a patient's quality of life, they are linked to a number of negative side effects. Oral mucositis is a common side effect in patients undergoing head and neck radiation therapy. While some chemotherapy-related side effects are being better managed, mucositis is becoming more common. Reducing patient risk factors, adopt proven preventative measures, and optimise supportive care practisespractices targeted to the patients' needs and symptoms are all recommendations that can be made. In clinical practisepractice and research, a variety of measures have been used to record the amount and severity of oral mucositis. The World Health Organization (WHO) scale is a simple, easy-to-use scale that can be used in clinical practisepractice on a regular basis. There's multiple approaches for management of Mucositis. Cryotherapy, palifermin, and sucralfate are among the three therapies that showed statistically significant effect in avoiding or lowering the severity of mucositis according to reports. In this article we'll be looking at Chemotherapy induced mucositis, its etiology, epidemiology, evaluation. And most importantly management

Introduction:

Oral mucositis is a severe ailment that causes erythema, edoema, and ulceration of the oral mucosa, as well as pain and oral intake restrictions. The lesions can also compromise the skin's barrier, allowing infection to spread locally or systemically. In severe situations, this may necessitate parenteral feeding, resulting in a lower quality of life. [1] Oral mucositis is a common side effect of cancer treatment. It starts 5-10 days after chemotherapy starts and lasts 7-14

Comment [SS1]: oedema

Comment [SS2]: rather say ...are frequently utilised...

Comment [SS3]: delete

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Comment [SS5]: There are

Comment [SS6]: Does not need to be capitalized.

Comment [SS7]: oedema

days. Oral mucositis caused by chemotherapy causes the mucosal lining of the mouth to atrophy and break down, resulting in ulcers. [2]

Comment [SS8]: Reword please.

Most patients undergo chemotherapy as an outpatient, but if they develop fever and neutropenia, an apparent infection, or another problem, they are admitted to the hospital. Chemotherapy, whether at standard doses or in higher-dosed myeloablative protocols used in conditioning regimens (with or without total body radiation in preparation for hematopoietic cell transplantation), frequently causes erythema, edoema, atrophy, and ulceration of the oral mucosa, a condition known as oral mucositis. Oral mucositis causes pain and restricts oral intake, necessitating complete parenteral nutrition and increased usage of narcotic analgesics in severe cases (e.g., patients undergoing myeloablative therapy prior to HCT). [2]

Comment [SS9]: as outpatients

Comment [SS10]: oedema

Comment [SS11]: State it in full first with abbreviation in bracket. Subsequently use abbreviation.

Chemotherapy and radiation therapy are the most often utilised cancer treatment options. Despite the fact that these treatments are used to improve a patient's quality of life, they are linked to a number of negative side effects. Patients suffer from severe adverse responses as a result of these therapies, resulting in morbidity and mortality. Furthermore, they contribute to the affected patient's economic ramifications. Approximately 400,000 cases of treatment-induced injury to the oral cavity occur each year. Mucositis (stomatitis); xerostomia (dry mouth); bacterial, fungal, or viral infection (especially in neutropenic patients); dental caries; loss of taste; and osteoradionecrosis are some of the oral problems associated with chemotherapy and/or radiation therapy. [3]

While some chemotherapy-related side effects are being better managed, mucositis is becoming more common. Reduce patient risk factors, adopt proven preventative measures including using oral ice chips with fluorouracil chemotherapy, and optimise supportive care ~~practises~~practices targeted to the patients' needs and symptoms are all recommendations that can be made. The examination of a number of new experimental drugs, notably those directed to the epithelial mucosa, such as mitogens and epithelial growth factors, has resulted from progress in understanding the pathophysiology of mucositis at the molecular level. In preclinical trials, these appear to be highly promising. In the coming years, randomised clinical trials using these medications may eventually show an impact on the clinical ~~practise~~practice of mucositis care. [4]

Comment [SS12]: Use present continuous tenses eg "Reducing patient's risk factors...P

General Etiology of mucositis & Risk Factors:

Oral mucositis is a common side effect in patients undergoing head and neck radiation therapy, chemotherapy for solid tumours or lymphoma, or high-dose myeloablative chemotherapy prior to hematopoietic cell transplantation. Oral mucositis is more common with some chemotherapy drugs than others. Oral mucositis is common with chemotherapeutic drugs that disrupt DNA Synthesis (S-phase), such as 5-fluorouracil, methotrexate, and cytarabine. Oral mucositis is a serious side effect of anthracyclines, mTOR inhibitors, alkylating drugs, and antimetabolites. Chemotherapeutic drugs can cause mucositis in two ways: directly and indirectly. [1,5-8]

Comment [SS13]: Elaborate on the direct and indirect ways further.

Age, nutritional state, kind of cancer, oral care during therapy, and neutrophil count before treatment are all key risk factors. Mucositis is more common in younger people due to a faster epithelium mitotic rate or the presence of more epidermal growth factor receptors. Poor oral hygiene has been linked to the development of mucositis after chemotherapy and/or radiation therapy, according to certain research. The incidence and severity of mucositis have been shown to be reduced when ill-fitting dental prostheses are repaired, periodontal disease is eliminated, and problematic teeth are extracted, all while maintaining good oral hygiene. There is always the risk of inadequate mucosal regeneration in nutritionally impaired patients, which can lead to the development of severe mucositis. Because haematological tumours have more protracted and strong myelosuppression, chemotherapy-induced mucositis is more prevalent (depending also on the chemotherapeutic agent given) Because of the direct irradiation of the mouth cavity, radiation-induced mucositis is prevalent in head and neck tumours (depending also on the dose and type of radiation) [3,9-11]

Comment [SS14]: Needs references.

Comment [SS15]: Needs reference

Epidemiology:

Mucositis occurs at different rates and severity depending on the chemotherapeutic agent, the number of chemotherapy cycles, the chemotherapy dose, and the patient. Oral mucositis is more common in patients who receive myeloablative preparations for hematopoietic stem cell transplant. [1]

Approximately 40% of cancer chemotherapy patients develop some form of oral mucositis. Oral mucositis develops in at least 75% of patients undergoing myeloablative conditioning regimens (chemotherapy with or without total body

irradiation) in preparation for HCT; the rate may be much higher in children. Patients who undergo continuous infusion therapy for breast and colon cancer, as well as those who receive adjuvant therapy for head and neck cancers, have a greater incidence. The incidence of oral mucositis in patients of the same age with similar diagnoses and treatment regimens and identical oral health condition can, however, vary significantly. This is most likely due to genetic differences as well as other factors that have yet to be fully identified or understood. [2]

Radiation-induced oral mucositis (RIOM) affects 100 percent of patients treated with altered fractionation radiation for head and neck cancer. Mucositis is more common in patients who are malnourished and have poor oral hygiene. Oral mucositis is more common in patients who are younger.[1]

Comment [SS16]: Better use "majority"

Comment [SS17]: Needs a reference

Mucositis severity and duration are related to the radiation source, cumulative dosage, dose intensity, volume of radiated mucosa, smoking, alcohol use, and oral hygiene in patients receiving radiation therapy. In individuals treated with typical 200 cGy daily fractionated radiation treatments, mucosal erythema develops during the first week. During the fourth to fifth weeks of treatment with the same dose of radiation, patchy or confluent mucositis peaks. The severity of mucositis is expected to be modest with daily fractionated regimens of less than 200 cGy. Mucositis, on the other hand, peaks 3 weeks after radiation therapy in rapid radiotherapy programmes. Interstitial radioactive implant-induced mucositis usually occurs in 7 to 10 days and peaks after 2 weeks. [3,12-14]

Evaluation:

Mucositis is graded by the World Health Organization (WHO) as follows: For the evaluation of mucositis, this scoring system is commonly utilised in ordinary clinical practise and clinical trials. It is scored on a scale of 0 to 4. It is evaluated as 0 if the patient has no indications or symptoms. It is classified as 1 if the patient experiences painless ulcers, edoema, or mild soreness. It is classified as 2 if there is painful erythema, edoema, or ulcers but you may eat. It is classified as 3 if there is painful erythema, edoema, or ulcers but no ability to eat. It is classified as a 4 if parenteral or enteral assistance is required. [3]

Comment [SS18]: oedema

Comment [SS19]: oedema

Comment [SS20]: oedema

In clinical ~~practise~~practice and research, a variety of measures have been used to record the amount and severity of oral mucositis. The World Health Organization (WHO) scale is a simple, easy-to-use scale that can be used in clinical

[practisepractice](#) on a regular basis. This scale combines subjective and objective oral mucositis measurements. Mucositis has separate subjective and objective scales in the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The Mouth Mucositis Assessment Scale (OMAS) is an objective scale that measures erythema and ulceration at nine different places in the oral cavity for research purposes. In a multi-center trial, this scale was found to have great inter-observer reliability and a substantial association between objective mucositis scores and patient complaints. Oncology trials use the Eastern Cooperative Oncology Group (ECOG) standard toxicity criteria to document the severity of oral mucositis. [15]

Comment [SS21]: Elaborate more on this system as this is the system oncologists use to report adverse effects. I think the latest version is version 5.

Toxicology criteria for evaluating stomatitis from the National Cancer Institute: This scale is also rated on a scale of one to four. The grade for painless ulcers, erythema, or moderate tenderness is 1. It is scored as 2 when the patient exhibits painful erythema, edoema, and ulcer but is able to eat. It is evaluated as 3 when there is an incapacity to consume. A patient who requires parenteral or enteral nutrition is given a grade of 4. [3]

OAG (oral assessment guide): This is a crucial tool for determining the severity of mucositis. Validity and interreliability testing have been carried out on it. Researchers can evaluate the effectiveness of different oral care regimes and identify persons at risk for stomatitis problems when changes in oral cavity status as a result of chemotherapy and/or radiation therapy are measured using reliable and valid OAG. It consists mostly of eight components, each of which is ranked from 1 to 3. [3]

Comment [SS22]: delete

Comment [SS23]: Long an confusing sentence. Use shorter and clearer sentences.

Management:

A series of reviews on the prevention of oral mucositis caused by radiotherapy and/or chemotherapy have been published in the Cochrane Library. Worthington et al. found that only ten interventions (aloe vera, amifostine, cryotherapy, granulocyte colony-stimulating factor (G-CSF), intravenous glutamine, honey, keratinocyte growth factor, laser irradiation, polymyxin / tobramycin / amphotericin (PTA) antibiotic tablet / paste, and sucralfate) are effective in preventing or reducing mucositis. Cryotherapy, palifermin, and sucralfate were the only three therapies that showed statistically significant effect in avoiding or lowering the severity of mucositis. It should be noted that cryotherapy was only

studied in patients with haematological malignancies who had received chemotherapy or stem cell transplantation; palifermin was studied in patients who had received radiotherapy, stem cell transplantation, chemotherapy, or a combination of these treatments; and sucralfate was studied in patients who had received radiotherapy. [16]

It has been proposed that freezing the oral mucosa with ice chips reduces blood flow to the mucosa, hence limiting the availability of chemotherapeutic drugs to the mucosa. The North Central Cancer Treatment Group (NCCTG) compared the effects of 5FU-based chemotherapy against no treatment on 95 patients undergoing their first round of treatment. Stomatitis was reduced by nearly 50% in patients who had oral cryotherapy. However, there are no corroborating studies that we are aware of. [3]

Pain is the most common symptom of oral mucositis. This pain has a substantial impact on dietary intake, oral hygiene, and overall quality of life. As a result, managing mucositis discomfort is an important part of any mucositis management approach. Saline mouth rinses, ice chips, and topical mouth rinses with an anaesthetic, such as 2 percent viscous lidocaine, are used in many centres. Equal amounts of lidocaine and diphenhydramine, as well as a soothing covering agent like Maalox or Kaopectate, might be combined. These topical anaesthetics may provide temporary relief. [15]

Cryotherapy is one of the most widely utilised therapies for the prevention of oral mucositis, especially in patients taking short-half-life chemotherapeutic drugs such as 5-fluorouracil, edatrexate, and melphalan. The administration of cryotherapy 5-30 minutes before and for 20-30 minutes (even up to 6 hours, according to some studies) following the 5-fluorouracil bolus dosage dramatically lowers oral mucositis in individuals treated with 5-fluorouracil. [16-24]

Allopurinol's metabolite, oxypurinol, inhibits an enzyme involved in pyrimidine production, causing orotic acid to accumulate intracellularly. The activation of 5FU to fluorouracil monophosphate is inhibited by this chemical, which reduces 5FU toxicity. Although initial pilot trials conducted by Bleyer demonstrated that allopurinol mouthwashes were effective, research undertaken by the NCCTG revealed that patients receiving the allopurinol mouthwash saw an increase in 5FU-induced mucositis. [3]

Comment [SS24]: What was compared? 5FU vs no 5FU? Or cryotherapy vs no cryotherapy?

Other topical mucosal bioadherent treatments that are not anaesthetics but are thought to alleviate pain by creating a protective covering over ulcerated mucosa are also available. Sucralfate has been the subject of the most research. Because of its lack of efficacy, the MASCC/ISOO guidelines advise against using sucralfate in radiation-induced oral mucositis. Due to a lack of consistent outcomes, no recommendation has been made for the use of sucralfate in chemotherapy-induced oral mucositis. Most patients with severe mucositis, in addition to topical medications, require systemic analgesics, which commonly include opioids, to achieve adequate pain relief. For patients undergoing hematopoietic cell transplantation, the MASCC/ISOO recommendations propose patient-controlled analgesia with morphine. [15,25-27]

Growth Factors and Cytokines: Wu et al. investigated the role of recombinant human epidermal growth factor (RhEGF) in the reduction of OM. A total of 113 patients were enrolled in the study, all of them were receiving chemoradiotherapy. At the primary outcome, RhEGF dramatically reduced the occurrence of severe OM. A comparable investigation was carried out by Kim et al. A total of 138 patients were split into two groups: control—placebo and RhEGF therapy. There was no statistically significant difference between these groups, according to the findings of this study. As a result, both investigations yielded contradictory results, necessitating the conduct of additional, more in-depth research. [28-30]

Anti-Inflammatory Drugs: Kazemian et al. examined the effect of benzydamine oral rinse (a non-steroidal anti-inflammatory medicine) on radiation-induced mucositis prophylaxis. The trial included 100 patients who were randomly assigned to one of two groups: benzydamine or placebo. The results showed that 43.6 percent of the benzydamine group had mucositis grade III or above, compared to 78.6 percent in the placebo group. In the placebo group, grade III mucositis was 2.6 times more common. Also, Rastogi et al. have examined the impact of this drug on the prevention of OM caused by radiotherapy and chemotherapy. A total of 120 people took part in the survey. The results showed that patients who received radiation and benzydamine oral rinse experienced grade III OM less frequently than the control group. The chemotherapy-treated individuals, on the other hand, provided no statistically significant data. [28,31,32]

Comment [SS25]: State in full first and put abbreviation in bracket. Thereafter use the abbreviation.

Conclusion:

While some chemotherapy-related side effects are being better managed, mucositis is becoming more common. Imposing real challenge when it comes to management of chemotherapy side effects. Luckily there's multiple treatments that can be effective both for preventive and management measures. Among these method Cryotherapy, palifermin, and sucralfate are among the three therapies that showed statistically significant effect in avoiding or lowering the severity of mucositis. We hope for developing of new and more effective management methods as well as more studies that can be made to assess the efficacy of current ones.

Comment [SS26]: You earlier said sucralfate showed inconsistent results and that MASCC/ISOO advises against using it.

Comment [SS27]: Change to "... the development of..."

Comment [SS28]: Change to "...should be done..."

UNDER PEER REVIEW

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