Review Article

Management of Chemotherapy induced Mucositis

Abstract:

Oral mucositis is a severe ailment that causes erythema, edema, and ulceration of the oral mucosa, as well as pain and oral intake restrictions. Chemotherapy and radiation therapy are the most often utilized 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 optimize supportive care practices targeted to the patients' needs and symptoms are all recommendations that can be made. In clinical 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 practice on a regular basis. There are 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, edema, 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 days. Chemotherapy-

induced oral mucositis causes the mucosal lining of the mouth to atrophy and break down, resulting in ulcers [2]

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, edema, 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]

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 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 practice of mucositis care. [4]

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. [1,5-8]

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 [3]. 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 [9]. There is always the risk of inadequate mucosal regeneration in nutritionally impaired patients, which can lead to the development of severe mucositis [10]. 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) [11]

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 majority 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]

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 practice 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, edema, or mild soreness. It is classified as 2 if there is painful erythema, edema, or ulcers but you may eat. It is classified as 3 if there is painful erythema, edema, or ulcers but no ability to eat. It is classified as a 4 if parenteral or enteral assistance is required. [3]

In clinical 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 practice on a

regular basis. This scale combines subjective and objective oral mucositis measurements. 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]

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, edema, 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. It consists mostly of eight components, each of which is ranked from 1 to 3. [3]

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 mucosit. 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. [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 mouthrinses 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]

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 hematopoetic 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]

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. 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.

References:

1. Bell A, Kasi A. Oral Mucositis. [Updated 2021 Apr 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK565848/
2. Nathaniel S Treister; Chemotherapy-Induced Oral Mucositis. Jun 22, 2017. Medscape. https://emedicine.medscape.com/article/1079570-overview
3. Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. Neoplasia. 2004 Sep-Oct;6(5):423-31. doi: 10.1593/neo.04169. PMID: 15548350; PMCID: PMC1531648.
4. Knox JJ, Puodziunas AL, Feld R. Chemotherapy-induced oral mucositis. Prevention and management. Drugs Aging. 2000 Oct;17(4):257-67. doi: 10.2165/00002512-200017040-00002. PMID: 11087004.
5. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB., Mucositis Study Section of the Multinational Association for Supportive Care in Cancer. International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004 May 01;100(9 Suppl):1995-2025.

6. Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. Neoplasia. 2004 Sep-Oct;6(5):423-31.
7. Valer JB, Curra M, Gabriel AF, Schmidt TR, Ferreira MBC, Roesler R, Evangelista JMC, Martins MAT, Gregianin L, Martins MD. Oral mucositis in childhood cancer patients receiving high-dose methotrexate: Prevalence, relationship with other toxicities and methotrexate elimination. Int J Paediatr Dent. 2021 Mar;31(2):238-246.
8. Barasch A, Peterson DE. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. Oral Oncol. 2003 Feb;39(2):91-100.
9. Sonis S, Costa JW, Jr, Evitts SM, Lindquist LE, Nicolson M. Effect of epidermal growth factor on ulcerative mucositis in hamsters that receive common chemotherapy. Oral Surg Oral Med Oral Pathol. 1992;74:749–755.
10. Lichtman SM. Physiological aspects of aging—implication for the treatment of cancer. Drugs Aging. 1995;7:212–225.
11. Sonis ST. In: Oral complication of cancer therapy: Principles and Practices of Oncology. Devita VT, Hellman R, Rosenberg, SA, editors. Philadelphia, PA: Lippincott; 1993. pp. 2385–2394.
12. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. Eur J Cancer. 1992;28:457–462.
13. Verdi CJ. Cancer therapy and oral mucositis—an approval of drug prophylaxis. Drug Saf. 1993;9:185–195.
14. Baker DG. The radiobiological basis for tissue reactions in the oral cavity following therapeutic X-irradiation. Arch Otolaryngol. 1982;108:21–24.
15. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent Clin North Am. 2008 Jan;52(1):61-77, viii. doi: 10.1016/j.cden.2007.10.002. PMID: 18154865; PMCID: PMC2266835.
16. Chaveli-López B, Bagán-Sebastián JV. Treatment of oral mucositis due to chemotherapy. J Clin Exp Dent. 2016 Apr 1;8(2):e201-9. doi: 10.4317/jced.52917. PMID: 27034762; PMCID: PMC4808317.
17. Nikoletti S, Hyde S, Shaw T, Myers H, Kristjanson LJ. Comparison of plain ice and flavoured ice for preventing oral mucositis associated with the use of 5 fluorouracil. J Clin Nurs. 2005;14:750–3.

18. Baydar M, Dikilitas M, Sevinc A, Aydogdu I. Prevention of oral mucositis due to 5-fluorouracil treatment with oral cryotherapy. J Natl Med Assoc. 2005;97:1161–4.
19. Sorensen JB, Skovsgaard T, Bork E, Damstrup L, Ingeberg S. Double-blind, placebo-controlled, randomized study of chlorhexidine prophylaxis for 5-fluorouracil-based chemotherapy-induced oral mucositis with nonblinded randomized comparison to oral cooling (cryotherapy) in gastrointestinal malignancies. Cancer. 2008;112:1600–6.
20. Papadeas E, Naxakis S, Riga M, Kalofonos C. Prevention of 5-fluorouracil-related stomatitis by oral cryotherapy: A randomized controlled study. Eur J Oncol Nurs. 2007;11:60–5.
21. Lilleby K, Garcia P, Gooley T, McDonnnell P, Taber R, Holmberg L. A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2006;37:1031–5.
22. Vokurka S, Bystricka E, Scudlova J, Mazur E, Visokaiova M, Vasilieva E. The risk factors for oral mucositis and the effect of cryotherapy in patients after the BEAM and HD-l-PAM 200 mg/m(2) autologous hematopoietic stem cell transplantation. Eur J Oncol Nurs. 2011;15:508–12.
23. Karagözoğlu S, Filiz Ulusoy M. Chemotherapy: the effect of oral cryotherapy on the development of mucositis. J Clin Nurs. 2005;14:754–65.
24. Clarkson JE, Worthington H V, Furness S, McCabe M, Khalid T, Meyer S. Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev. 2010:CD001973
25. Dodd MJ, Miaskowski C, Greenspan D, et al. Radiation-induced mucositis: a randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes. Cancer Invest. 2003;21(1):21–33.
26. Nottage M, McLachlan SA, Brittain MA, et al. Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. Support Care Cancer. 2003 Jan;11(1):41–47.

27. Barasch A, Elad S, Altman A, Damato K, Epstein J. Antimicrobials, mucosal coating agents, anesthetics, analgesics, and nutritional supplements for alimentary tract mucositis. Support Care Cancer. 2006 Jun;14(6):528–532.
28. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, Filipauskas A. Prevention and Treatment of Chemotherapy and Radiotherapy Induced Oral Mucositis. Medicina (Kaunas). 2019 Jan 22;55(2):25. doi: 10.3390/medicina55020025. PMID: 30678228; PMCID: PMC6410239.
29. Therapeutic effect of recombinant human epidermal growth factor (RhEGF) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer: a double-blind placebo-controlled prospective phase 2 multi-institutional clinical trial. Wu HG, Song SY, Kim YS, Oh YT, Lee CG, Keum KC, Ahn YC, Lee SW Cancer. 2009 Aug 15; 115(16):3699-708.
30. Topical Recombinant Human Epidermal Growth Factor for Oral Mucositis Induced by Intensive Chemotherapy with Hematopoietic Stem Cell Transplantation: Final Analysis of a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial. Kim JW, Kim MG, Lee HJ, Koh Y, Kwon JH, Kim I, Park S, Kim BK, Oh JM, Kim KI, Yoon SS PLoS One. 2017; 12(1):e0168854.
31. Kazemian A., Kamian S., Aghili M., Hashemi F.A., Haddad P. Benzydamine for prophylaxis of radiation-induced oral mucositis in head and neck cancers: A double-blind placebo-controlled randomized clinical trial. Eur. J. Cancer Care (Engl.) 2009;18:174–178. doi: 10.1111/j.1365-2354.2008.00943.x.
32. Rastogi M., Khurana R., Revannasiddaiah S., Jaiswal I., Nanda S.S., Gupta P., Chufal K.S., Bhatt M.L. Role of benzydamine hydrochloride in the prevention of oral mucositis in head and neck cancer patients treated with radiotherapy (>50 Gy) with or without chemotherapy. Support. Care Cancer. 2017;25:1439–1443. doi: 10.1007/s00520-016-3548-9.