Treatment-induced mucositis in oncology

Abstract

Almost all cancer therapies lead to a wide array of side effects, owing to the disruption of normal physiological processes and alteration of immunological responses. Of these, mucositis is one of the most commonly encountered side effects, presenting in about 20–40% of all patients receiving chemotherapy and 80% of those being treated with radiotherapy for head and neck malignancies. This article provides a brief introduction and comprehensive overview of the various treatment modalities used in managing this complication. The key to management is a multidisciplinary approach, revolving around pain control, oral hygiene, nutritional support and management of superimposed infection. The scarcity of therapeutic options for prevention or treatment of mucositis has resulted in clinical difficulty in controlling it, which, in turn, seriously affects the patient's quality of life and cancer management, contributing to patient morbidity and mortality.

Key words: Chemotherapy; Mucositis; Oncology; Radiotherapy; Side effects

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Introduction

Mucositis is an inflammatory and ulcerative condition affecting the oral and gastrointestinal mucosa (Isozaki and Brant, 2022). It is one of the most common side effects of cancer treatment, being experienced to some degree by up to 40% of all patients receiving chemotherapy, 80% of patients receiving radiotherapy for head and neck malignancies and 100% of bone marrow transplant patients receiving high-dose chemotherapy (Thomsen and Vitetta, 2018). This, in turn, can lead to a reduction in quality of life and survival rates, intolerance to treatment and increased treatment costs for affected patients (Rao et al, 2021; Sougiannis et al, 2021). Given the prevalence and potential significant consequences, this article provides a summary of treatment-induced mucositis in cancer patients, to assist in its prevention, diagnosis and management.

Definition

In 2007, the term 'mucositis' was adopted to describe lesions associated with chemotherapy and/or radiotherapy cytotoxic effects. It is characterised by atrophy of squamous epithelial tissue, vascular damage and an inflammatory infiltrate concentrated at the basement region. Epithelial atrophy is followed by ulceration, which then becomes covered with fibrinous-inflammatory (pseudomembranous) exudate, leading to the condition termed 'ulcerative/pseudomembrane mucositis' or 'pseudomembranous mucositis'. Mucositis is considered to be an inevitable, yet transient, side effect of anti-neoplastic therapies (European Association of Oral Medicine, 2022).

Pathogenesis

The pathogenesis for mucositis was previously thought to be a direct consequence of the effect of anti-cancer agents on rapidly dividing cells in the body. However, it is now considered to be caused by a wide array of molecular mechanisms, broadly labelled as inflammation, which are involved in perpetuating the initial insult imposed by chemoradiotherapy. A complex interaction of local tissue damage, alongside patient-related factors, such as levels of immunosuppression and genetic predisposition, accounts for the effects seen.

A five-phase model has been proposed to possibly explain the pathology, comprising:

1. Initiation
2. Upregulation and activation

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3. Signal amplification
4. Ulceration
5. Healing.

This process is initiated by direct DNA injury, which leads to a state of oxidative stress, causing cell damage in the basal epithelial, submucosal and endothelial cells. This is the key step that leads to upregulation of the inflammatory pathway by activating macrophages and important signalling pathways. These include nuclear factor (NF)-κβ and distinct pathogen-associated molecular patterns, such as toll-like receptors (Shankar et al, 2017). These also contribute to amplification of the entire process by the activation of the positive feedback loops. For example, tumour necrosis factor (TNF)-α activates NF-κβ, mitogen-activated protein kinase (MAPK) and sphingomyelinase pathways, while also contributing directly to cellular and tissue injury. The result is erythema from increased vascularity and epithelial atrophy, manifesting 4–5 days after the initiation of chemotherapy. Minor forms of trauma from daily activities, such as speech, swallowing and mastication, lead to ulceration. This increases the chances of bacterial contamination. The final phase is characterised by healing, where cell proliferation takes place, with re-epithelialisation of the ulcers (Bonomi and Batt, 2015).

Causes

The incidence and severity of mucositis depends on chemotherapy regimen, doses and treatment timing. Antimetabolites, platin-derived drugs, taxanes, anthracyclines, irinotecan and alkylating agents can all promote mucositis to varying degrees. The risk of developing mucositis rises when chemotherapy is associated with radiotherapy. Radiotherapy alone is the most significant risk factor, as any therapeutic dose of radiation to the gastrointestinal mucosa essentially causes some form of mucositis in almost all patients. Again, the severity of this phenomenon is influenced by the dosing and frequency of treatment regimens (Pulito et al, 2020).

Clinical significance

Mucositis has a number of impacts on the clinical management of cancer patients, some of which are described below:

- Pain is the most commonly encountered problem during the clinical course of mucositis, with patients frequently requiring high doses of parenteral opioid therapy. In certain groups of patients, such as those with head and neck cancers, it can lead to reduced oral intake and weight loss, necessitating alternative feeding methods, which are associated with their own potential complications
- Oral mucositis is a major risk factor for systemic infections in patients who are already prone to infections, owing to their cancer. Those undergoing high-dose chemotherapy before stem cell transplantation are at an even higher risk of sepsis, because of their profound immunosuppression. This can, in turn, lead to an increase in the number of hospitalisations, delayed treatments and infection-related deaths (Çakmak and Nural, 2019)
- Rates of hospitalisation as a result of severe mucositis have been reported as 32% for altered fractionation radiotherapy and 16% of all types of radiotherapy (European Association of Oral Medicine, 2022)
- Alteration and interruption of planned chemotherapy regimens, secondary to the above complications, can lead to suboptimal treatment of the patient's malignancy.

Risk factors

Several risk factors that increase the chances of developing mucositis and associated infections have been identified. These include:

- Poor oral hygiene
- Smoking or chewing tobacco
- Alcohol consumption
- Reduced salivary secretions before and during treatment
- Sex (women tend to have a higher incidence than men)
- Dehydration

- Low body mass index
- Comorbidities, such as kidney disease, diabetes or HIV/AIDS
- Previous cancer treatment
- Chronic irritation from ill-fitting prostheses or faulty restorations.

Generally, patients with haematological malignancies have an increased rate of oral mucositis compared to those with solid tumours. This is, to some extent, related to the differing treatment regimens for these conditions (Oral Cancer Foundation, 2022).

Diagnosis and grading

Mucositis is a clinical diagnosis based on reported symptoms and examination findings (Sanches et al, 2020), with no reliable biomarkers identified to assist in the prediction or diagnosis of onset (Pulito et al, 2020). Most of the literature concerning diagnosis and grading of severity of mucositis relates to oral mucositis (that is, mucositis affecting specifically the oral mucosa), owing to the difficulty in directly observing the pathological changes to the gastrointestinal mucosa in gastrointestinal mucositis (Lalla and Bowen, 2018). Therefore, both oral and gastrointestinal mucositis are discussed separately below.

Oral mucositis

The initial presentation of oral mucositis is as erythema of the oral mucosa, which can then progress to erosion and ulceration. In chemotherapy-induced mucositis, these lesions tend to be limited to the tongue, buccal mucosa and soft palate, whereas, in radiotherapy-induced mucositis, the lesions are limited to mucosa within the radiation field. These physical signs are demonstrated in Figures 1a and b. The main reported symptom of oral mucositis is pain, which can then lead to functional impairment in speech and oral intake. The lesions may resolve within 10–18 days of cessation of chemotherapy; however, in the case of radiation-induced mucositis, lesions may take several weeks to resolve (Lalla and Bowen, 2018).

There are several grading scales used to determine the severity of oral mucositis. Two of the most widely used scales are presented in Tables 1 and 2.

Gastrointestinal mucositis

Symptoms of gastrointestinal mucositis include abdominal pain, bloating, nausea and diarrhoea. These symptoms often manifest within 1 week of commencing chemotherapy, and tend to resolve by the end of the second week following the chemotherapy dose. Given

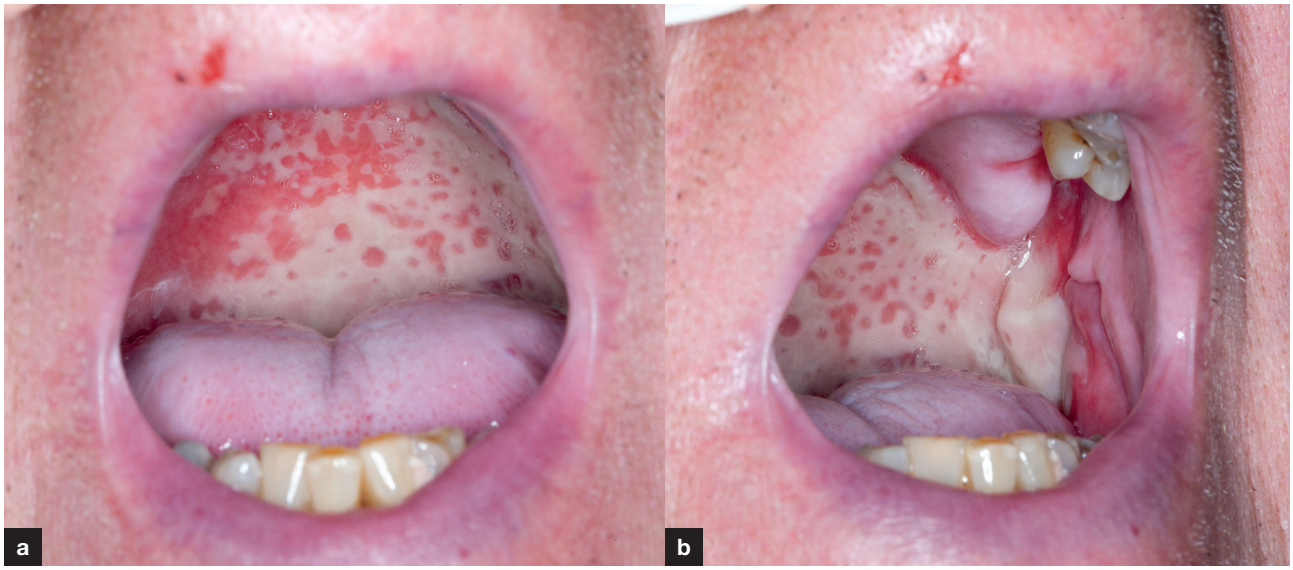

Figure 1. a and b. Erythema and ulceration of the oral mucosa in a patient receiving concurrent chemoradiotherapy for a head and neck malignancy.

Table 1. The World Health Organization's oral mucositis scale

Grade	Description
Grade 0 (none)	None
Grade 1 (mild)	Oral soreness, erythema
Grade 2 (moderate)	Erythema, ulcers; solid diet tolerated
Grade 3 (severe)	Oral ulcers; liquid diet only
Grade 4 (life-threatening)	Oral feeding is impossible, requires parenteral nutrition

Adapted from World Health Organization (1979)

Table 2. The National Cancer Institute's common terminology criteria for adverse events

Grade	Description
Grade 0 (none)	None
Grade 1 (mild)	Asymptomatic or mild symptoms; intervention not indicated
Grade 2 (moderate)	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated
Grade 3 (severe)	Severe pain; interfering with oral intake
Grade 4 (life-threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (death)	Death

Adapted from National Cancer Institute (2018)

that invasive investigations would be required to observe mucosal changes during this period, the grading of gastrointestinal mucositis tends to be correlated with the severity of symptoms, particularly diarrhoea (Lalla and Bowen, 2018).

Treatment and prevention

Given the potentially significant negative clinical impact of mucositis on a patient's treatment and quality of life, prevention is a key part of the management of mucositis. There is a wide range of suggested preventative and treatment strategies for mucositis, the evidence for which is collated and analysed by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) to produce evidence-based guidelines stratified by disease and treatment type (Elad et al, 2020). These guidelines are discussed below, grouped by category of treatment.

Basic oral care

As discussed above in relation to risk factors, poor oral hygiene has been found to predispose a patient to oral mucositis (Chen et al, 2021). Basic oral care refers to non-pharmacological methods to optimise the health of the oral mucosa to thereby reduce this risk.

Patient education

Maintaining good oral hygiene requires the patient to understand and implement the necessary skills to look after their teeth appropriately, as it is the patient who will be managing their own oral care most of the time (Carra et al, 2020). The use of soft toothbrushes, biotene toothpaste and non-irritating mouthwashes is recommended to minimise irritation of the oral mucosa; these can be supplied alongside educational materials to assist the patient in developing positive oral hygiene habits, such as regular flossing (Cullen et al, 2018). Although the MASCC and ISOO review found insufficient evidence on this to form a guideline, the panel recommends that patient education is likely to provide some benefit with regards to the patient adhering to oral care protocol throughout their treatment (Hong et al, 2019).

Professional oral care

Despite the MASCC and ISOO review finding that there is, again, insufficient evidence on professional oral care to form a guideline, it is also suggested that assessment and treatment by dental professionals before the commencement of anti-cancer treatment would likely be of benefit in the prevention of severe oral mucositis, as it provides an opportunity to treat any pre-existing oral health problems, as well as to give targeted education on oral care (Niikura et al, 2020). It should be noted that dental procedures should be avoided during radiotherapy to the head and neck area, because of the increased risk of complications and poor healing. This is another reason that thorough dental assessment should be commenced before treatment (Herrick et al, 2021).

Bland mouth rinses

The term 'bland mouth rinses' refers to products that do not contain medically active ingredients. Sodium chloride (saline) and sodium bicarbonate mouth rinses are both frequently used in the prevention and treatment of oral mucositis, with a frequency of 4–6 mouth rinses per day recommended to keep the oral mucosa moist and, thereby, less friable, as well as promoting oral clearance (Huang et al, 2018; Madeswaran and Jayachandran, 2018). Although there was insufficient evidence to suggest benefit in the prevention and treatment of mucositis, the MASCC/ISOO panel advised that bland mouth rinses would likely be beneficial in achieving a positive impact on oral hygiene and patient comfort (Hong et al, 2019).

Chlorhexidine

Chlorhexidine is a topical antiseptic with broad-spectrum antimicrobial effects, widely used in the treatment of gingivitis. Although it has been proposed that the bactericidal, fungicidal and virucidal effects of chlorhexidine mouthwash would help to reduce the risk of secondary infections in oral mucositis, systematic reviews have not shown any evidence for a statistically significant reduction in incidence or severity of oral mucositis in patients regularly using chlorhexidine (Cardona et al, 2017). It has even been suggested that the use of chlorhexidine by patients receiving radiotherapy for head and neck cancers can result in greater susceptibility to unpleasant side effects, including discomfort, taste alteration and teeth staining (Foote et al, 1994). This led to the MASCC/ISOO review recommending against the use of chlorhexidine in this patient population (Hong et al, 2019).

Risk factor modification

Aside from oral hygiene, other risk factors that can be modified include cigarette smoking, alcohol consumption and poor diet. As these can all irritate the oral mucosa, any reduction in intake will reduce the risk or severity of oral mucositis (Thomas et al, 2019).

Anti-inflammatory agents

As described above, inflammation plays a key role in the pathogenesis of mucositis. Therefore, it follows that anti-inflammatory agents would play a role in the management of mucositis. Despite this, benzydamine hydrochloride mouthwash is the only topical anti-inflammatory agent with sufficient evidence to suggest benefit. However, this beneficial effect has only been adequately demonstrated in the prevention of oral mucositis in head and neck cancer patients receiving radiotherapy or concurrent chemoradiotherapy, at a dose of 10–15 ml four times a day (Chitapanarux et al, 2018). There is insufficient evidence to demonstrate benefit in the treatment of oral mucositis, or in the prevention of mucositis, in other disease groups (Ariyawardana et al, 2019).

Photobiomodulation

Photobiomodulation refers to the use of lasers or sources of light to beneficially impact cellular metabolism through exposure of the mucosal cells to photons. Although a full explanation of the theory behind this intervention is beyond the scope of this article, it is worth noting that there is a growing evidence base demonstrating benefit in both the prevention and treatment of oral mucositis in various patient groups, including those receiving radiotherapy, chemoradiotherapy and haematopoietic stem cell transplantation (Cronshaw et al, 2020).

Other treatments for oral mucositis

The above treatments are the mainstay of prevention and treatment of oral mucositis, with photobiomodulation representing a relatively new and rapidly developing treatment possibility, which is likely to be more frequently used in the future. Many other agents and techniques have been used in the prevention and treatment of oral mucositis, to varying degrees of success. This article does not have the capacity to discuss all possible treatments, and the MASCC/ISOO guidelines (Hong et al, 2019) should be consulted for a complete list of recommendations and suggestions. The broad categories are briefly mentioned below, with some more widely used examples (Elad et al, 2020).

Cryotherapy

This is only recommended in patients undergoing haematopoietic stem cell transplantation using particular chemotherapy regimens.

Topical analgesics

Morphine mouthwash is suggested as a possible treatment for oral mucositis-associated pain in head and neck cancer patients receiving chemoradiotherapy.

Coating agents

Sucralfate is not recommended for the prevention or treatment of pain associated with oral mucositis in any patient groups.

Natural agents

Oral glutamine may be beneficial in patients with head and neck cancers receiving radiotherapy, but should not be used parenterally in patients undergoing haematopoietic stem cell transplantation. Honey may also be beneficial in the prevention of oral mucositis.

Treatments for gastrointestinal mucositis

All of the treatments discussed thus far specifically relate to oral mucositis, which is representative of the significantly larger proportion of research being carried out into mucositis affecting the oral cavity, as opposed to the rest of the gastrointestinal tract, which is likely related to the difficulties in diagnosing and quantifying gastrointestinal mucositis (Sougiannis et al, 2021). Most of the treatment guidelines produced by MASCC/ISOO (Hong et al, 2019) relate to gastrointestinal mucositis secondary to radiotherapy targeting the pelvis. These are discussed briefly below (Elad et al, 2020):

- Intravenous amifostine: This should be used for the prevention of radiation proctitis. Oral sulfasalazine may also be beneficial
- Oral sucralfate: This should not be used to treat gastrointestinal mucositis caused by radiotherapy; however, given as an enema, it may be beneficial in treating chronic proctitis associated with rectal bleeding
- Oral 5-acetylsalicylic acid and misoprostol suppositories should not be given for acute radiation proctitis
- Octreotide: This should be used to treat diarrhoea, refractory to loperamide in patients receiving high dose-chemotherapy associated with haematopoietic stem cell transplantation.

Nutritional support

One of the main risks related to severe oral mucositis is the reduction in oral intake, which can lead to malnutrition, dehydration and subsequently poorer health outcomes. Multidisciplinary assessment of patients experiencing mucositis is essential to avoid these complications, particularly through regular assessments by dietitians to ensure nutritional requirements are being met. As the oral mucositis increases in severity, and oral intake of food or even nutritional supplements becomes intolerable, enteral feeding may be required, and care must be taken to avoid potential refeeding syndrome (Arends, 2018). Early nutritional support reduces the risk of malnutrition, thereby assisting the patient to achieve better overall health outcomes, as well reducing the risk of severe oral mucositis (Wei et al, 2020).

Key points

- Mucositis is one of the most common side effects of anti-cancer therapies.
- Mucositis is a significant cause of disrupted anti-cancer treatment and reduced quality of life. It can be caused by both chemotherapy and radiotherapy, and severity of symptoms is impacted by intensity of the treatment regimen.
- Mainstays of prevention of mucositis include basic oral care, mouthwashes and risk factor reduction, although few interventions demonstrate significant benefit in the treatment of mucositis. Nutritional support is required in many cases of mucositis, so early involvement of dietitians is essential.

Conclusions

Mucositis is one of the most significant adverse effects of anti-cancer therapies, because of its prevalence and possible consequences on patient quality of life and further treatment. Although many treatment modalities have been used to try and mitigate the negative impact of mucositis on cancer patients receiving treatment, very few of these show benefit in the treatment of mucositis that has already developed. There is a lack of large randomised controlled trials to support the use of many of the interventions routinely implemented in cancer centres across the world. Although photobiomodulation presents a promising possibility, lack of widespread access to the necessary equipment and expertise means that supportive measures, such as basic oral care and benzydamine mouthwash, continue to be the mainstay of mucositis management at present.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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