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Review

Prevention, Evaluation, and Treatment of Chemotherapy and Radiotherapy Induced Oral Mucositis

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Abstract

Oral mucositis is a frequent adverse effect of cancer treatment that includes radiotherapy (RT) and chemotherapy (CT). It is related to worse outcomes because of pain, nutritional problems, effects on quality of life, changes in cancer treatment, the risk of infection, and financial costs. It affects 20% to 80% of people receiving chemotherapy, and almost all patients receive head and neck radiation therapy. This review presents the current understanding and discusses evidence-based clinical management strategies for oral mucositis. The current model of mucositis pathogenesis is comprised of five broad stages. The two widely used grading systems for routine clinical care and research on mucositis are the WHO (World Health Organization) and Oral Mucositis Scale and the National Cancer Institute's Common Toxicity Criteria (NCI-CTC). The effective use of assessment scales, nonpharmacologic treatment modalities such as good professional oral hygiene, cryotherapy, and photobiomodulation, and pharmacologic therapies such as KGF-1 (palifermin) and benzydamine-containing mouthwash are important for mucositis prevention, and topical morphine is effective for the treatment of mucositis induced by radiotherapy or chemotherapy. Mucoadhesive hydrogel and anti-inflammatory medications such as celecoxib, misoprostol, and rebamipide are reported to be effective for radiation-induced mucositis. However, additional experimental studies are required to confirm the evidence.

Keywords: *oral mucositis, cancer, treatment, radiotherapy, chemotherapy*

Introduction

Oral mucositis is an inflammation and ulceration of the oral cavity caused by systemic chemotherapy and/or radiation therapy used to treat cancer. It affects 20% to 80% of people receiving chemotherapy, and almost all patients receive head and neck radiation therapy (1, 2). The morbidity of oral mucositis might include discomfort, dietary problems, quality-of-life issues, changes in cancer treatment, the risk of infection, and financial difficulties. Oral mucositis is associated with longer hospital stays and increased mortality in immunosuppressed patients (3-5).

The pathophysiological process of oral mucositis is complex, and this condition majorly affects nonkeratinized mucosa, particularly the buccal mucosa, soft palate, floor of the mouth, lateral edges of the tongue, and lips (6). The current model of mucositis pathogenesis is comprised of five broad stages (7), such as the initiation stage, signaling stage, amplification stage, ulceration stage, and final healing stage. Radiotherapy or chemotherapy initially causes cellular damage and free radical production, which leads to the destruction of the basal epithelial cells. Increases in inflammatory substances, which exacerbate cell death, occur after it. Mucosal ulcerations are brought on by pro-inflammatory cytokine upregulation and hasten the spread of a secondary infection. Epithelial proliferation, cellular differentiation, and tissue differentiation all occur in the final stage. The severity of mucositis depends on different factors like the anticancer treatment regimen, age, oral hygiene, and genetic characteristics (8).

The WHO Oral Toxicity Scale and NCI-CTC for Adverse Events are the two scales that are most frequently used to rate the severity of oral mucositis. The WHO scale (9, 10) includes Grade 1—soreness with or without erythema; Grade 2—erythema with painful ulcers; Grade 3—ulcers with extensive erythema; being unable to swallow solid foods; bleeding; Grade 4—ulcers with extensive erythema; alimentation not possible. According to the NCI-CTC for Adverse Events, death is considered as Grade 5 (11).

To prevent, treat, or reduce the severity of mucositis, considerable research has been conducted worldwide. The International Society for Oral Oncology (ISOO) and the Multinational Association of Supportive Care in Cancer (MASCC/ISOO) created guidelines in 2004 (12), and the authors last revised their recommendations in 2020. This study offers the most convincing data and details the clinical situation in which these interventions are most likely to be beneficial (13). Even if oral mucositis is one of the major adverse effects associated with conventional radiotherapy or chemotherapy, true evidence-based clinical practice protocols for the prevention and management strategies of oral mucositis are still lacking. This review presents the current understanding of the management and prevention strategies of mucositis and discusses evidence-based clinical management strategies for oral mucositis.

Methodology

On November 26, 2022, a thorough literature search was undertaken in the Pubmed and Cochrane databases using the medical subject headings (MeSH) and a combination of all relevant terms that were listed in the databases. The reference lists of the previously mentioned studies were used as a starting point for a manual search for publications through Google Scholar to avoid missing any potential study. We looked for useful information in publications, primarily clinical trial studies that covered evidence about interventional and preventive strategies for chemo-radiotherapy-induced oral mucositis. Language and participant age were both unrestricted.

Discussion

Grading scales of oral mucositis assessment

The WHO Oral Mucositis Scale and the National Cancer Institute's Common Toxicity Criteria (NCI-CTC) **(Table 1)** are the two most widely utilised grading systems for routine clinical care and research in mucositis. The WHO grading system is frequently used in both regular clinical practice and experimental studies. The WHO scale ranges from 1 to 4. Both scales are simple to use and may be applicable to patients undergoing radiotherapy or chemotherapy. Both scales assign grades based on factors such as pain, the presence of erythema and ulceration, and the type of diet. Other grading systems also exist, which include the Oral Mucositis Index and the Oral Mucositis Assessment Scale, which use a combination of objective, functional, and symptomatic variables (14). Unfortunately, there is not one universally accepted standard for assessment, and, as a result, interpretation across clinical studies is often difficult.

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Table 1: Grading scales of oral mucositis

	WHO (10)	NCI-CTC (11)
GRADE 1	Oral soreness, erythema	Asymptomatic or mild symptoms; intervention not indicated
GRADE 2	Erythema, ulcers; patient can swallow solid food	Moderate pain; not interfering with oral intake; modified diet indicated
GRADE 3	Ulcers with extensive erythema; patient cannot swallow food	Severe pain interfering with oral intake
GRADE 4	Mucositis to extent that alimentation not possible	Life-threatening consequences; urgent intervention indication
GRADE 5	NA	Death

NA: Not applicable, WHO: World Health Organisation, NCI: National Cancer Institute's Common Toxicity Criteria

Prevention and Treatment Strategies

The severity and length of mucositis symptoms during chemoradiotherapy management are decreased by the availability of numerous therapeutic medications. The following section of the article makes an effort to review the many preventative and therapeutic approaches to this illness. However, due to polypharmacy, heterogeneity, and the generally small patient groups in clinical trials, evaluating various modalities is challenging. In addition, the majority of studies that have been done have relied on arbitrary scoring systems. There are surprisingly few studies that evaluate pathological testing as unbiased measurements. It is generally recognized that individuals with head and neck cancer, whether they receive chemotherapy or not, can develop radiation-induced oral mucositis; hence, prevention measures are crucial. The following are the primary methods and medications listed in the literature for preventing and/or treating oral mucositis secondary to chemo-radiotherapy

Oral Hygiene

Oral care is a low-cost intervention that is frequently recommended to decrease oral microbe activity and amount as well as to prevent or diminish discomfort related to oral mucositis. Oral hygiene can reduce the presence of microbial flora, reduce pain and bleeding, and prevent infection. Good oral health also reduces the likelihood of dental problems. Even though there is not a universal recommendation for oral care guidelines in the most recent clinical practice guidelines, empirical evidence from single studies suggests that a standardized and consistent oral care routine within a facility may be able to prevent or reduce the severity or duration of oral mucositis (6, 15, 16). In contrast to self-care, Saito et al. (17) showed that regular professional oral health care decreased the probability of oral mucositis in chemotherapy patients. The incidence of ulcerative mucositis decreased by 38%, according to Cheng et al. (18), who investigated the efficiency of an oral care routine. Additionally, the reduction in severity and associated discomfort were also noted in their investigation. Several recommendations were made regarding the use of multiagent combination oral care procedures to prevent oral mucositis during cancer treatment. Many empirical studies have suggested that oral hygiene recommendations and supplements containing mineral derivatives like zinc sulfate may have helped avoid or decrease the symptoms of oral mucositis, particularly when receiving oncological treatment (19). The updated MASCC/ISOO recommendations suggest following a routine oral care routine that includes using a soft toothbrush, flossing, and non-medicated rinses such as sodium bicarbonate or saline rinses (20). The significance of good oral hygiene should be made clear to patients and caregivers.

Cytokines and growth factors

Growth factor agents, including keratinocyte growth factors (KGF), recombinant human epidermal growth factor (RhEGF), colony-stimulating factors (CSF), transforming growth factor-beta (TGF-), and trefoil factor (TFF), have been proposed to improve the course of mucositis.

The keratinocyte growth factor is used effectively to treat chemo-radiotherapy-induced oral mucositis because of its strong cytoprotective properties for epithelial cells (21, 22). Palifermin, a recombinant human KGF, is the first medication to be authorized by the FDA to decrease the duration and frequency of mucositis in cases with hematologic malignancies receiving high-dose chemotherapy and needing HSCT, as well as to likely reduce the risk of oral mucositis in adults receiving both radio-chemotherapy for head and neck cancer, or CT or RT alone (23-25). FGF-20 (velafermin) and human recombinant KGF-2 (repifermin), two other KGF family members, have overlapping activities with KGF-1 but

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may also carry out additional functions that impact their effectiveness.

Regarding the effect of RhEGF, studies reported conflicting findings. A considerable decline in the incidence of severe oral mucositis was reported by Wu et al. (26). However, another RCT by Kim et al. (27) revealed that RhEGF was regarded as beneficial if the grading of oral mucositis was ≤1.

According to Stokman et al.'s meta-analysis (28), systemic G(M)-CSF may prevent oral mucositis. However, Worthington et al. (23) concluded that there is only little support for the idea that systemic or topical G-CSF may help patients with H&N cancer receive RT to avert severe oral mucositis. Additionally, MASCC/ISOO recommendations concurred that there is inadequate data to support or disprove the use of subcutaneous G-CSF for reducing mucositis in cases receiving CT (29). It has been proven that KGF1 (palifermin) is useful for preventing oral mucositis in a specific therapeutic environment. Likewise, the argument against using topical GM-CSF to prevent mucositis is supported by the previously reported data (30).

Anti-inflammatory medication

Nonsteroidal anti-inflammatory drugs have a long history of being used safely in cancer patients with mucositis. Anti-inflammatory drugs can inhibit proinflammatory cytokines such as TNF and IL-1. Patients getting RT in a moderate dose for head and neck cancer are routinely prescribed benzydamine, a powerful anti-inflammatory medication, for pain relief when they develop oral mucositis (31, 32). To avert oral mucositis in cancer patients receiving moderate-dose RT, there is sufficient clinical evidence to advise them to use benzydamine mouthwash (31, 33, 34). Epstein et al. demonstrated that head and neck cancer patients receiving RT at cumulative doses up to 50 Gy experienced less severe mucositis after using benzydamine hydrochloride mouthwash (35). In these patient groups, however, there is insufficient evidence for hematologic and solid tumor chemotherapy prevention.

Other experimental anti-inflammatory medications include celecoxib (36), misoprostol (37), and rebamipide (38). However, evidence for its therapeutic properties in radiation-induced mucositis is either lacking or insufficient (39).

Antimicrobials, Anesthetics, Analgesics, and Coating Agents.

A wide range of potentially harmful microorganisms, including gram-positive and gram-negative pathogenic bacteria and fungi, are present in the oral mucosa of cancer patients. Several antimicrobial agents have been studied for oral mucositis, including antibacterial, antiviral, and antifungal agents. In the antimicrobial product subgroup, the use of chlorhexidine (40), smecta (41), actovegin (42), and kangfuxin (43) resulted in significant therapeutic and preventive effects; however, comparing the effectiveness of these products would be challenging due to the disparate assessment criteria and treatment protocols selected by researchers.

Topical morphine has been found effective in several RCTs. Studies reported its efficacy in reducing mucositis severity, with a greater reduction in the extent and intensity of pain as well as the extent of functional impairment (44-46).

In an RCT, the effectiveness of mucoadhesive hydrogel for mucositis treatment was compared to a sham control. The area under the curve of daily patient-reported mouth discomfort and WHO scores on the final day of RT shows that the medication successfully reduced OM symptoms (47). It justifies the addition of mucoadhesive gel to the treatment arsenal for patients receiving standard RT regimens for head and neck cancer. However, no additional studies have been published to back up the evidence.

The MASCC/ISOO recommendation advises against the use of antimicrobial lozenges, chlorhexidine mouthwash, and iseganan mouthwash for oral mucositis because of the lack of reliable evidence of their effectiveness (48); Additionally, the following medications are not advised for radiation-induced mucositis: bacitracin, doxepin, amphotericin B (PTA) paste, polymyxin, sucralfate, tobramycin, and mouthwash containing doxepin (13, 49).

Laser therapy

The effectiveness of photobiomodulation (PBM) has been demonstrated in well-designed clinical trials and may be regarded as a patient-friendly therapy option, particularly for children who might have trouble adhering to traditional treatments like mouthwash. With a strong base of evidence, the MASCC/ISOO guidelines advise using PBM to avoid oral mucositis brought on by chemotherapy and radiotherapy.

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A recent meta-analysis published after the latest update of MASCC/ISOO included recently emerging evidence to support the efficacy of photobiomodulation in the management of cancer chemotherapy-induced oral mucositis (50). Their findings illustrated that photobiomodulation is an effective therapeutic intervention for reducing oral mucositis severity, so it is advised for the treatment (50). The use of extra- and intra-oral lasers on patients receiving RT for head and neck cancer resulted in improved clinical outcomes and a decrease in oral mucositis (51). To assess the patient's risk of relapse and overall survival, long-term follow-up is needed. Additionally, the expensive laser equipment, the requirement for ongoing maintenance, and the requirement for staff training are the drawbacks of PBM (50).

Cryotherapy

Freezing the oral mucosa with ice chips can reduce blood flow to the mucosa and, as a result, decrease the accessibility of chemotherapeutic medications to the mucosa. Studies on cryotherapy have shown promising outcomes in the treatment and prevention of chemo-radiotherapy-induced oral mucositis (40). Cryotherapy is recommended by the MASCC/ISOO guidelines as a way to treat oral mucositis in patients getting bolus doses of 5-fluorouracil as well as in those receiving high-dose melphalan for HSCT (52). In theory, cryotherapy could be useful to reduce oral mucositis caused by any chemotherapy drug with a short half-life that is administered during a short period (53).

Conclusion

The effective use of assessment scales, nonpharmacologic treatment modalities such as good professional oral hygiene, cryotherapy, and photobiomodulation, and pharmacologic treatments such as KGF-1 (palifermin) and benzydamine mouthwash is important for the prevention of mucositis, and topical morphine is beneficial for the treatment of mucositis induced by RT or CT. Mucoadhesive hydrogel and anti-inflammatory medications such as celecoxib, misoprostol, and rebamipide are reported to be effective for radiation-induced mucositis. However, additional experimental studies are required to confirm the evidence.

Disclosure

Conflict of interest

There is no conflict of interest

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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