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Review Article

Oral Mucositis, a Side Effect of Hematological Malignancies Treatment

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Abstract

Oral mucositis is painful inflammation of oral mucosa and one of the most common side effects of chemotherapy, radiotherapy and hematopoietic stem cells transplantation. As the damaged mucosa is very painful, it causes problems in oral intake of food and beverages. Oral mucositis significantly impairs patients' quality of life and may affect the outcome of hematological malignancy treatment. This paper presents a review of published data on the pathogenesis, clinical picture, complications, and therapy and prevention of oral mucositis in patients treated for hematological malignancies. The most significant factor for the development of oral mucositis is the type and intensity of antineoplastic therapy and use of agents that damage oral mucosa. Best prophylaxis is implementation of professional oral hygiene measures and motivation of patients to maintain good individual oral hygiene and avoid harmful habits which damage oral mucosa, such as alcohol and smoking, at least during antineoplastic therapy.

Keywords: Oral Mucositis; Chemotherapy; Radiotherapy; Hematological Malignancies; Oral Hygiene

Abbreviations

DNA: Deoxyribonucleic Acid; TLR: Toll Like Receptor; TNF: Tumor Necrosis Factor; MSC: Mesenchymal Stem Cell Transplantation; HSV: Herpes Simplex Virus; LLLT: low Level Laser Therapy; HSCT: Hematopoietic Stem-Cell Transplantation.

Introduction

Mucositis is a painful inflammatory condition with erosive and ulcerative lesions of the oral and gastrointestinal mucosa. It occurs as a complication of chemotherapy, radiotherapy and hematopoietic stem cell transplantation. The clinical picture of mucositis varies from mild erythema to extensive ulcerations that can affect the mucosa of all parts of the digestive tract. Since mucositis can affect the entire digestive tract, it is divided into: oral mucositis - which affects the mucous membrane of the oral cavity, gastrointestinal mucositis - which affects the gastric and intestinal mucosa, and mucositis of the digestive tract - which affects the entire mucous membrane of the digestive tract [1]. Mucositis is caused by damage to cellular DNA. Highly proliferative cells of the oral epithelium are particularly susceptible leading to increased apoptosis of mature and reduced formation of new cells. Mucositis occurs in 20-40% treated patients with solid tumors [2]. incidence is even higher during treatment of malignant hematological diseases; in the transplantation of hematopoietic stem cells it occurs in as many as 80% of patients [3].

Neutropenia, which occurs as a side effect of anticancer treatment, increases the susceptibility of oral mucosa to infections caused by oral microflora, which further worsens mucositis.

Oral mucositis is most often localized at the base of the oral cavity, the lateral edges of the tongue, the buccal mucosa and the soft palate. Oral mucositis significantly worsens the quality of life of patients, causes pain, makes speech and normal nutrition difficult, and complicates the treatment of the primary disease. Therefore, dentists should be members of the multidisciplinary team for the treatment of all tumors, especially hematological [4].

Pathogenesis of oral mucositis

In earlier papers on adverse effects associated with the development of mucositis, the role of tissue structures (extracellular

matrix and tight joints), inflammatory mediators, and microbiome was mainly considered [5]. Recent works are increasingly analyzing the toxicity of specific antitumor substances and conditions, markers of mucosal injury and risk factors for the development of mucositis.

Microbiome and host immune response

Changes in the composition of the oral microbiome occur during development of oral mucositis, but accurate identification of bacterial species has become possible only with technological advances and the possibility of sequencing the bacterial genome. Dynamic changes of bacterial species as a consequence of antitumor treatment play an important role in the development of both intestinal and oral mucositis [6].

In vitro studies on oral keratocytes have shown that radiotherapy leads to a change in the composition of the microbiome, and that changes in the microbiome in turn affect the healing process [7].

The potential for targeted action on microbial-mucosal interactions has been demonstrated in murine knock-out models of mucositis. Toll-like receptors (TLRs) are the focus of these studies because they are the site of interaction of bacterial ligands and signaling cascades in immune, neural and epithelial cells [8]. TLR agonists may in some cases protect against mucositis. Studies in laboratory mice have shown that the TLR5 agonist, CBLB502, reduces the intensity of radiation-induced oral mucositis [9].

It is not yet entirely clear whether TLR agonists directly protect the epithelium or do so through resident microbes. Evidence for the latter is the fact that consumption of probiotics improves healing of mucosal injuries resulting from antitumor treatment [10]. A potential mechanism could be related to TLR receptor agonism with gram-positive species such as *Lactobacillus* spp [11].

However, due to the variability in the results of clinical trials of probiotics, further research is needed to elucidate the impact of microbial-mucosal interaction on the pathogenesis of mucositis.

Inflammatory agents

Inflammation and pro-inflammatory cytokines that activate the NF-κB signaling pathway play an important role in the pathogenesis of oral mucositis [12]. Attempts to treat mucositis by blocking these pathways with pentoxifylline or celecoxib have not been successful [13].

Expression of the Smad 7 protein, an antagonist of NF-κB and TNF-β1, in transgenic mice has been shown to be effective in preventing radiation-induced oral mucositis [14]. Local administration significantly reduced epithelial cell apoptosis. Anti-oxidative enzymes such as superoxide dismutases have also been shown to provide protection against mucositis because they antagonize formation of free radical oxygen and nitrogen compounds that are mediators of inflammation [15].

Mesenchymal stem cell transplantation (MSC) in laboratory mice has shown good results in the treatment of radiation-induced oral mucositis, but its success depended on the time of transplantation [16].

While new data suggest that natural immune cells also play a role in preventing oral mucositis in patients with transplanted hematopoietic stem cells [17], there are still many open questions on the role of congenital and acquired immunity in the pathogenesis of oral mucositis [18].

Clinical features of oral mucositis

Clinical features of oral mucositis include erythema and ulcerations of oral mucosa accompanied by pain and difficulty in swallowing and speech. Damaged mucosa often bleeds. Ulcers are susceptible to infection that can remain localized or spread systemically. Symptoms usually appear 5 to 8 days after start of chemotherapy and subside 7 to 14 days after its discontinuation, but according to patients, the total recovery time of mucosa and restoration of normal oral function in conventional cyclic chemotherapy can be up to 4 weeks [19].

Complications of oral mucositis

Pain

Intense pain associated with ulceration is the most common complication of oral mucositis. Most patients need systemic opioid analgesics for pain control. According to study by Sonis., *et al*. in patients with hematopoietic stem cell transplants, each additional stage of oral mucositis was associated with 2.6 additional days of intravenous opioid therapy [20].

Difficulty taking food

Patients with advanced oral mucositis can not eat normally due to pain. They therefore need parenteral or feeding through a nasogastric tube. Increase in one degree of oral mucositis severity was associated with 2.7 additional days of parenteral nutrition in

hematopoietic stem cell transplant patients [20]. Patients treated for head and neck tumors who develop oral mucositis, on average lose more than 5% of body weight [21]. Insufficient nutrient intake makes these patients more susceptible to infection and compromises immunity and the success of antitumor therapy.

Impact on quality of life

Pain and inability to eat normally reduce the quality of life. This is particularly seen in patients undergoing head and neck tumor radiotherapy and those receiving high doses of chemotherapeutics prior to hematopoietic stem cell transplantation. Those patients cite oral mucositis as the most debilitating side effect of chemotherapy [22].

Impact on primary disease therapy

Oral mucositis may lead to dose reduction or discontinuation of antitumor therapy. In patients with lymphoma and solid tumors who had mucositis in the previous cycle, the next dose of chemotherapy was reduced twice as often as in those who did not. In 11% of patients irradiated for head and neck tumors, unplanned interruptions in therapy occurred due to advanced mucositis [23]. Discontinuation or change of antitumor treatment regimen worsens the outcome of the treatment and prognosis of the primary disease.

Susceptibility to infections:

Ulcers of oral mucositis are colonized by the oral microflora and are occasionally complicated by local infections, such as herpes simplex virus [HSV] infection or candidiasis. In immunosuppressed patients due to chemotherapy, these ulcerated lesions may become entry for microbiota causing sepsis that can be life-threatening. For example, in patients receiving chemotherapy for lymphoma or solid tumors, the incidence of infections is twice as high in cycles of chemotherapy with the onset of mucositis than in those without. The intensity of infections was proportional to the severity of mucositis. Mortality due to infection was also higher in chemotherapy cycles in which mucositis occurred. In patients treated with high doses of chemotherapy prior to hematopoietic stem cell transplantation, the occurrence of moderate or advanced oral mucositis correlated with systemic infections and transplant mortality. Exacerbation of oral mucositis increases the likelihood of systemic infection, the number of days with fever and increases the likelihood of mortality in the first 100 days after transplantation by 3.9% [3].

Impact on oral health

Patients with oral mucositis have difficulty maintaining normal oral hygiene by brushing their teeth and flossing. Permanent or temporary hyposalivation is also a common consequence of antitumor therapy. These two factors together increase the incidence of dental caries or periodontal disease. In addition, due to immunosuppression, lesions of oral mucositis are often secondarily infected with HSV or *Candida spp* [24].

Economic impact

Oral mucositis is associated with an increase in the cost of antitumor treatment itself. Research conducted in the U.S. shows that pain control medications, parenteral nutrition supplements, gastric tube probes, secondary infections, and hospitalizations increase treatment costs by $ 1,700-6,000 per patient, depending on the progression of mucositis. In patients treated with conventional doses of chemotherapy, hospitalization costs were 60% higher for cycles after which mucositis developed. According to the research an increase in the severity of oral mucositis is associated with a 2.6-day longer hospital stay and an increase in hospital costs by $ 25,000 [25].

Mechanisms of action of hematological disease on the oral mucosa

Patients with hematological diseases develop oral complications two to three times more often than patients with solid tumors [26]. They are caused by one of the three main mechanisms. The first is a direct consequence of leukemia in which a disrupted immune system and leukemia cells directly attack the oral tissues. The second mechanism is a consequence of specific therapy and occurs due to the direct effect of the drug on the oral mucosa. The direct toxic effect on the tissues of the oral cavity is due to the non-specific action of the drug on cells in mitosis. These drugs affect not only the replication of tumor cells but also those of healthy tissue. Consequently, the possibility of basal epithelial regeneration is reduced resulting in oral epithelial atrophy, mucositis, and ulceration. The third mechanism is an indirect consequence of myelosuppression. Antioneoplastic drugs act on hematopoietic cells of the bone marrow causing thrombocytopenia and granulocytopenia, which makes the already damaged oral mucosa more prone to bleeding and infections. elevated levels of TNF α and interleukin-6 in the blood and genetically induced changes in cellular apoptosis [27].

Impact of oral mucositis on hematological disease treatment

Oral mucositis significantly affects the quality of life, causes a feeling of discomfort and burning, pain and problems with food intake. Oral lesions can also be a source of systemic spread of infection and a cause of septicemia. Hematological patients with oral mucositis are four times more likely to develop septicemia than patients without it [28]. Patients with serious oral complications often need more intensive hospital care, enhanced medication, parenteral nutrition, and longer hospital stays [29]. Therefore, prevention and management of oral complications are important for improving the quality of life of the patient and successful oncological treatment.

Risk factors for the development of oral mucositis

Individual risk factors for the development of oral mucositis differ in different studies. However, there is no doubt that higher intensity or duration of chemotherapy or radiotherapy is the main risk factor for severe mucositis. In addition, most studies indicate damage to the oral mucosa due to smoking, excessive alcohol consumption or poor oral hygiene, etc. as unfavorable and dental remediation before starting antitumor treatment as a protective factor [30].

Effects of oral hygiene

Good oral hygiene is important for the overall health of the oral cavity and thus for the health of the oral mucosa. As hematological patients, due to exhaustion from the primary disease and its treatment, are often less motivated to maintain good oral hygiene, it is very important to warn them of its importance and the impact of oral health on overall health. A study by Kashiwazaki., *et al*. showed a significantly reduced probability of developing oral mucositis in patients who underwent professional oral hygiene measures prior to bone marrow transplantation [31]. Yokota., *et al*. investigated the association between individual oral hygiene and the severity the of oral mucositis. Despite teaching patients about individual maintenance of oral hygiene, 43% developed grade 3 or 4 oral mucositis according to the clinical findings and 53% according to subjective disorders. The results of this study showed that individual oral hygiene is not as effective in preventing a decrease in the severity of oral mucositis [32] because of severe pain and discomfort in the oral cavity and general poor condition of the patient.

Study by Đurić., *et al*. showed that implementing professional oral hygiene measures and restoration of carious teeth with patient motivation to maintain individual oral hygiene before a chemotherapy cycle partially alleviates subjective symptoms of discomfort in the mouth and dryness. In the same study, it was shown that such patients were less exposed to *C. albicans* infections or Gram(-)bacilli [33].

From these studies it can be concluded that the implementation of professional oral hygiene measures before chemotherapy and instructing patients to maintain individual oral hygiene during treatment is a good way to control the severity of oral mucositis and once again confirms the importance of the role of dentists in overall treatment of hematological diseases.

Prevention and treatment

Photobiostimulation

The advantages of laser therapy in the prevention and treatment of oral mucositis are numerous. Laser therapy is a non-invasive method that is very important for patients with poor general condition. The advantage of lasers is that they can also be transported which is important for hospitalized patients. This therapy is also very effective in pediatric patients who cannot cope with other protocols for the treatment of oral mucositis, for example by using mouthwash [34].

Treatment of the oral mucosa with low-dose laser therapy (LLLT) has been shown in anti-inflammatory studies on hamsters to accelerate the healing of mucosal damage [35].

Intraoral photobiostimulation has been shown to be effective in the prevention of oral mucositis and associated pain in a number of clinical trials [36-38].

A study using the full visible light spectrum of 400-900nm wavelengths showed that the use of red light of 625-660 nm wavelength was most effective in patients with HSCT [39].

In a review paper by Zadik., *et al*. [40] the impact of photobiostimulation on the prevention and treatment of oral mucositis is presented. They recommend two photobiostimulation protocols in hematopoietic stem cell transplant patients:

- Use of He-Ne laser with a wavelength of 632.8nm with a power of 31.25mW/cm^2 of tissue, illuminating an area of 0.8 cm^2 for 40 seconds at a time, energy of 1 J/cm^2 in 18 places on the oral mucosa for 5 days at a distance less than 1 cm from the tissue after completion of pre-transplant conditioning [39].

- Use of a diode laser with a wavelength of 650 nm, power 1 W/cm^2, illuminating an area of 0.04 cm^2 for 2 seconds at a time, with an energy of 2 J/cm^2, at 54-70 places on the oral mucosa for 7-13 days in tissue contact from the first day of conditioning to 2 days after transplantation [39].

On the other hand, MASCC/ISOO recommends the use of LLLT wavelengths of 650nm, 450mW and energy of 2J/cm^2 for the treatment and prevention of oral mucositis in patients treated with high-dose chemotherapy and hematopoietic stem cell transplantation and patients treated from head and neck tumors based on survey by Gautama., *et al*. [41]. In the LLLT-treated group, symptoms appeared later, and there was significantly less stage 4 mucositis compared to the control group. LLLT therapy has not been shown to be effective in preventing oral mucositis caused by other treatments. In addition to intraoral, the extraoral application of lasers is also being investigated. Two studies have shown the effectiveness of this form of photobiostimulation on the prevention of oral mucositis [42,43]. The advantage of extraoral use of lasers is that patients with pain and limited mouth opening in oral mucositis also more easily tolerate the possibility of treating a larger area within a reasonable time [44].

Given the small number of published papers, this approach cannot yet be recommended for routine use in clinical practice, and research is underway to define the best dose and strength of photobiostimulation (PBT).

So far, most PBT research has focused on prevention rather than treatment of mucositis. So far, there is no clinical evidence of the effectiveness of laser therapy on advanced disease, but research on this is ongoing.

Photobiostimulation does not cause significant side effects. Only 15% of patients have an acute burning sensation during diode laser therapy with a wavelength of 635 nm [45].

Cryotherapy

Oral cryotherapy significantly reduces the incidence of oral mucositis in patients treated from solid tumors with fluorouracil-containing chemotherapy and higher-intensity oral mucositis in patients treated with high doses of melphalan before HSCT [46].This was also confirmed by a study by Sorensen., *et al*. where patients kept crushed ice in their mouths for 45 minutes during chemotherapy. It was shown that the examined patients developed oral mucositis of intensity 3 or 4 much less often and that the overall duration of symptoms of oral mucositis was significantly shorter than in the control group [47].Oral cryotherapy is a very useful, safe and non-invasive procedure, with almost no side effects, of great value in preventing oral mucositis.

Anti-inflammatory agents

Because the inflammatory response to tumor therapy plays an important role in the pathogenesis of oral mucositis, anti-inflammatory agents are one of the methods of treatment and therapy. Benzidamine belongs to a group of NSAIDs that inhibit the production of proinflammatory cytokines: TNF-α and IL-1β. Benzidamine also has a topical analgesic and anesthetic effect. The MASCC/ISOO guidelines recommend rinsing the mouth with a benzidamine solution to prevent oral mucositis in patients treated for head and neck tumors with moderate doses of radiotherapy (up to 50 Gy) without concomitant chemotherapy [48].

The research of Kanzemian., *et al*. investigated the effect of bezidamine hydrochloride rinsing solution in the prevention of radiotherapy-induced oral mucositis. The incidence of grade 3 or higher oral mucositis was found to be 2.6-fold lower in patients treated with benzidamine solution than in the placebo group [49].

Benzidamine hydrochloride solution did not show a statistically significant effect in the prevention of mucositis caused by chemotherapy [50]. Prostagladin E2 has not been shown to be effective in preventing oral mucositis in patients treated with allogeneic bone marrow transplantation [51].

Antimicrobial agents

Of the antimicrobial agents used to prevent the development of oral mucositis, chlorhexidine [CHX] solution has been the most studied. Chlorhexidine is a topical antiseptic with bactericidal, fungicidal and virucidal action. It has a broad spectrum of action and kills most G (+) and G (-) bacteria within 30 s and reduces the risk of opportunistic infections [52].

A study by Sorensen., *et al*. examined the effect of chlorhexidine gluconate solution on the prevention and treatment of chemotherapy-induced oral mucositis. The results showed that in patients who rinsed with chlorhexidine gluconate solution, stage 3 or 4 oral mucositis was statistically less common than in the placebo group and that the symptoms of oral mucositis lasted shorter [47]. On the other hand, a meta-analysis by Cardon., *et al*. did not show a statis-

tically significant effect of chlorhexidine solution on oral mucositis caused by radiotherapy [53].

Growth factors

Growth factors that stimulate epithelial cell proliferation are useful in the treatment of ulceration in oral mucositis. In routine administration, the recombinant human keratinocyte growth factor -1 (KGF-1) is palifermin. The MASCC/ISOO recommends the intravenous use of palifermin to prevent oral mucositis in patients treated with high-dose chemotherapy and whole-body radiotherapy and those treated with hematopoietic stem cell transplantation [54]. The dose for patients receiving high-dose chemotherapy during hematopoietic stem cell transplantation and who are expected to develop grade 3 or 4 oral mucositis is 60 μg palifermin/kg/day for three days before conditioning and three days after pre-selection of hematopoietic stem cells [55]. On the other hand, the stimulation factor of granulocyte-macrophage colonies did not show an effect and its use is not recommended for the prevention of oral mucositis [56].

Grade	Description
0 [none]	None
1[mild]	Oral soreness, erythema
2 [moderate]	Oral erythema, ulcers, solid diet tolerated
3 [severe]	Oral ulcers, liquid diet only
4 [life-threatening]	Oral alimentation impossible

Table 1: WHO- gradation scale of oral mucositis [57,58]- the most common used scale in clinical evaluation of mucositis.

Conclusion

In conclusion, professional oral hygiene measures combined with good maintenance of individual oral hygiene and avoidance of nox, such as alcohol and cigarettes, appear to be the best prevention of oral mucositis. In some groups of patients, the use of lasers, cryotherapy and palifermin are beneficial. In contrast, there are no proven effective methods of treating developed mucositis.

Conflict of Interest

Authors declare no conflict of interest.

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