doi: 10.21860/medflum2022_280995

Novel approach to the therapy of oral mucositis: a review

Suvremeni pristup liječenju oralnog mukozitisa: pregledni rad

Danica Vidović Juras, Vlaho Brailo, Božana Lončar Brzak, Ana Andabak Rogulj, Ivana Škrinjar, Monika Burja*

University of Zagreb, School of Dental Medicine, Zagreb, Croatia

Abstract. Oral mucositis (OM) is a serious inflammation of the mucosa and occurs in patients with head and neck cancer (HNC) who are being treated with radiotherapy (RT) and/or chemotherapy (CT), and in patients undergoing hematopoietic stem cell transplantation (HSCT). The inflammation accompanied with painful ulcerations inside the oral cavity impairs its function making the basic functions like eating and speech hard or even impossible. It usually occurs at the end of the first week of RT and lasts for several weeks after cessation. The intensity of OM can sometimes lead to discontinuation of RT. The degree of mucositis regarding chemotherapy depends on the type of antineoplastic drug, therapeutic procedure, duration of the therapy and dose, as well as previous exposure of the oral cavity to toxic agents. Prolonged or repeated administration of lower doses of chemotherapy is associated with a higher chance of developing oral mucositis comparing to a bolus, while chronomodulation of chemotherapy reduces the possibility of mucositis without affecting antineoplastic activity. The treatment of OM is symptomatic, as there is still no effective treatment. In this review paper, several contemporary options for alleviating the symptoms of oral mucositis are listed.

Keywords: drug therapy; radiotherapy; stomatitis; therapeutics

Sažetak. Oralni mukozitis (OM) ozbiljna je upala sluznice i javlja se u bolesnika s karcinomom glave i vrata (HNC) koji se liječe radioterapijom (RT) i/ili kemoterapijom (CT) te u bolesnika koji su podvrgnuti transplantaciji hematopoetskih matičnih stanica (HSCT). Upala praćena bolnim ulceracijama unutar usne šupljine narušava njezinu funkciju, čineći osnovne funkcije poput prehrane i govora teškim ili čak nemogućim. Obično se javlja na kraju prvog tjedna radioterapije i traje nekoliko tjedana nakon prestanka. Intenzitet oralnog mukozitisa ponekad može dovesti do prekida radioterapije. Stupanj mukozitisa kod kemoterapije ovisi o vrsti antineoplastičnog lijeka, terapijskom postupku, trajanju terapije i dozi, kao i o prethodnoj izloženosti usne šupljine toksičnim agensima. Produljena ili ponovljena primjena nižih doza kemoterapije povezana je s većom šansom za razvoj oralnog mukozitisa u usporedbi s bolusom, dok kronomodulacija kemoterapije smanjuje mogućnost mukozitisa bez utjecaja na antineoplastično djelovanje. Liječenje oralnog mukozitisa je simptomatsko jer još uvijek nema učinkovitog lijeka. U ovom preglednom radu navodi se nekoliko suvremenih opcija za ublažavanje simptoma oralnog mukozitisa.

Ključne riječi: radioterapija; stomatitis; terapeutici; terapija lijekovima

***Corresponding author:**
Monika Burja
University of Zagreb,
School of Dental Medicine
Gundulićeva 5, 10000 Zagreb, Croatia
E-mail: mburja@sfzg.hr

http://hrcak.srce.hr/medicina

INTRODUCTION

Oral mucositis (OM) is a common side effect during the treatment of patients with head and neck cancer[1]. It develops in 97% of patients undergoing head and neck radiation therapy with or without adjuvant chemotherapy[2]. In addition to the treatment of head and neck cancer, OM also occurs in almost 98% of patients undergoing hematopoietic stem cell transplantation[3], and in at least 50% of patients treated with some form of chemotherapy[4]. Patients with mucositis, oral and gastrointestinal, may develop a range of serious clinical symptoms, including pain caused by ulcerations, nausea, vomiting, heartburn, diarrhea, constipation, malnutrition, and weight loss[5, 6]. According to Pulito et al. approximately 19% of patients with head and neck cancer treated with chemoradiotherapy will be hospitalized due to intense pain caused by severe OM, resulting in delayed antineoplastic treatment and a worse prognosis[7]. OM affects the quality of life and treatment outcome of an individual's underlying disease, poses a major clinical challenge for health professionals, and is additionally an economic burden for the community.

ETIOPATHOGENESIS

Head and neck irradiation usually following surgery, is administered alone or in combination with chemotherapy. Most patients receive an amount of radiation between 60-70 Gy, distributed over 5 weeks so that daily radiation dose is 2 Gy[1]. The cytotoxic effects of antineoplastic treatment with an inflammatory mucosal response result in mucositis, most commonly of the oral cavity and oropharynx, although mucositis can affect the entire mucosa of the gastrointestinal tract[7]. Factors that are most likely linked with intense mucositis in the oropharyngeal region are high mitotic activity of oral mucosal cells[8], complex oral microflora that compromises wound healing and daily microtraumatization of the oral mucosa during chewing and speech[9].

The development of OM is a complex and dynamic process that takes place through five phases: initial phase, response to primary damage, signal amplification, ulceration, and healing[10]. The initial phase occurs immediately after the application of radiation or chemotherapy which causes direct DNA damage. Disruption of double DNA strands activates the p53 apoptotic process enhanced by caspase as well as formation of the free radicals and Reactive Oxygen Species (ROS) which interfere with the normal replication of deoxyribonucleic acid. Cells that undergo apoptosis subsequently begin to release endogenous damage-associated pattern molecules (DAMPs) and are the primary response to damage associated with the second stage of mucositis development. During the same phase, mucositis-affected mucosal cells initiate transcription of genes involved in inflammatory processes, among which nuclear factor-κB (NF-κB) is a major protein complex that induces expression of various proinflammatory genes, including those encoding proinflammatory cytokines (e.g., IL-1β, IL-6, TNFα), leading to the progression of OM[7]. Afterwards, the phase of amplification occurs, which results in a creation of a larger number of proinflammatory cytokines, which further progresses tissue destruction. The stage of ulceration occurs when the mucosa loses its integrity and painful lesions appear, so the clinical manifestations of OM become obvious[6]. Due to the disruption of the mucosal integrity, the microorganisms enter the submucosal layer so that bacteria colonize unhindered, which leads to secondary infections and additional production of proinflammatory cytokines. Patient experience severe pain, and the risk of systemic infections such as septicemia or sepsis increases at this stage, especially in the immunocompromised patients. After cessation of radiation or chemotherapy, a healing phase occurs due to a signal from the submucosal extracellular matrix, which results in a clinically evident restoration of the normal appearance of the mucosa[11].

The dentist is not only important because of dental interventions but is also a key figure in educating the patient about basic oral care procedures to minimize OM and other oral consequences of RT, CT or HSCT.

CLINICAL MANIFESTATIONS

OM, as well as other oral complications, is dose-dependent and occurs when radiation doses are greater than 45 Gy. The intensity of complications depends on the location and volume of irradiated tissue, the total radiation dose, the size and number of fractions, patient's age, general condition of the patient and the concomitant use of chemotherapy. The first clinical sign of OM appears at the end of the first week of radiation in the form of white spots on the mucosa. In the third week of radiation, localized ulcerations covered with fibrin pseudomembranes that are prone to secondary infections begin to develop. OM peaks at the end of radiation (around the sixth or seventh week) and lasts for another 2-4 weeks after discontinuation of therapy when improvement gradually occurs[12]. As in chemotherapy treatment, the degree of mucositis depends on the type of antineoplastic drug, therapeutic procedure, duration of therapy, dose and concomitant therapy as well as previous exposure of the oral cavity to toxic agents. Prolonged or repeated administration of lower doses of chemotherapeutics has been associated with a higher chance of developing oral mucositis in comparison when taking a bolus, while chronomodulation of chemotherapy reduces the chance of developing mucositis without affecting antineoplastic activity. The risk of developing oral mucositis increases with the number of cycles. If there has been a previous episode of chemotherapeutic-induced oral mucositis, the chance of oral mucositis recurring is higher. Drugs that act on DNA synthesis (so-called S-phase-specific agents such as 5-fluorouracil, methotrexate and cytarabine) show the most pronounced stomatotoxic effects[13]. The list of chemotherapeutics, as well as indications for their use, can be found in Table 1. OM will occur earlier in patients on chemotherapy than in patients on radiotherapy and will more often affect non-keratinized mucosa. OM peaks 7-10 days after chemotherapy when erythema turns into ulcers and represents the most painful period for the patient. OM is gradually withdrawn within 2-3 weeks after cessation of chemotherapy but provided the patient does not have bone marrow suppression[14]. In patients receiving HSCT, additional risk factors for developing OM are higher body mass index, genetics, and total body radiation as part of a fitness regimen. As with chemo/radiotherapy, OM is a dose-limiting adverse effect for patients receiving conditioning regimen[15].

Among the multitude of scales for assessing the intensity of OM, the scale of the World Health due to its simplicity and ease applicability is most commonly in use. The gradation of OM according to this scale is based on the clinical finding of the mucosa and the functional status/ability to consume food. There are four degrees of OM: I (mild) – erythema and mucosal edema; II (moderate) – erythema and ulceration, the patient may eat solid foods; III (severe) – ulceration, the patient can eat liquid, but not solid food; IV (life-threatening) – the patient is in a need for a parenteral nutrition[16].

PREVENTIVE AND THERAPEUTIC PROCEDURES

There is still no drug or agent that can completely prevent and/or easily cure OM. Therefore, the treatment of OM remains symptomatic, aimed at relieving pain, preventing infection of oral lesions, and maintaining normal oral function[12]. OM is the most difficult-to-tolerate side effect of oncology treatment, which is why the treatment may be delayed or discontinued in many patients. Therefore, OM receives a lot of attention in scientific and professional circles dealing with the care of oncology patients such as Multinational Association for Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO). The MASCC/ISOO first issued guidelines for the treatment of OM in 2004 and updated them in 2009, 2014 and 2020. The guidelines are a summary of the best available scientific evidence, framed in a practical clinical context. The purpose of guideline is to provide clinicians with strong evidence-based recommendations for the treatment of OM. MASCC/ISOO recommends or suggests, depending on the level of evidence (LoE) interventions for the prevention or treatment of OM in a specific patient population[1]. Concise recommendations for the management of oral mucositis are shown in Table 2.

Table 1. Chemotherapeutics associated with development of oral mucositis[13, 40-55]

Drug name	Indications for use
Actinomycin D	Acute myeloid leukemia, Gestational trophoblastic neoplasia, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma, testicular cancer
Cisplatin	Gestational trophoblastic neoplasia, testicular, ovarian and bladder cancers, epithelial tumors of the head and neck, lung cancer and cervical cancer combined with radiotherapy
Docetaxel	Breast cancer, prostate cancer, non-small cell lung cancer, head and neck cancer, adenocarcinoma of
5-Fluorouracil	Breast cancer, colon cancer (palliative care)
Methotrexate	Active rheumatoid arthritis in adult patients, severe disabling psoriasis that does not have an adequate response to other forms of treatments, such as light therapy, photochemotherapy and retinoid therapy, severe psoriatic arthritis in adult patients.
Thioguanin	Acute lymphoblastic leukemia in childhood
Amsacrin	Acute myeloid leukemia
Doxorubicin	Breast cancer, lung cancer, Kaposi sarcoma, acute lymphocyte leukemia, lymphoma
Etoposide	Testicular cancer, small cell lung cancer, acute myeloid leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, ovarian cancer
Mitoxantrone	Acute leukemia, lymphoma, prostate and breast cancer, late stage of severe multiple sclerosis.
Bleomycin	Squamous cell cancer of head and neck regions, Hodgkin's lymphoma, testicular carcinoma, sclerosing agent for malignant pleural effusions, childhood Hodgkin's lymphoma.
Cytarabine	Acute lymphocyte leukemia, chronic myeloid leukemia, non-Hodgkin lymphoma
Daunorubicin	Acute myeloid leukemia, acute lymphoblastic leukemia, neuroblastoma, rhabdomyosarcoma
Floxouridine	Hepatic metastases from colon cancer
Vindesine	Childhood acute lymphoblastic leukemia, multiple myeloma in adults, locally invasive or metastatic breast cancer

Table 2. Recommendations for management of oral mucositis.

Type of mucositis	Therapeutic option
Radiotherapy-induced mucositis	Polyvinylpyrrolidone sodium-hyaluronate gel Benzydamine Fentanyl nasal spray (opioid analgesic) Zinc-chloride based mouthwash Avasopazem manganese (Phase III clinical trials)
Chemotherapy-induced mucositis	Polyvinylpyrrolidone sodium-hyaluronate gel Photobiomodulation Cryotherapy 0.2% topical morphine mouthwash (opioid analgesic)
Chemo- and radiotherapy induced mucositis	Polyvinylpyrrolidone sodium-hyaluronate gel Photobiomodulation Honey Turmeric based gel or mouthwash
Mucositis in HSCT patients	Polyvinylpyrrolidone sodium-hyaluronate gel Photobiomodulation Palifermin (keratinocyte growth factor-1)

ORAL CARE

Oral care is a key factor in preventing and alleviating OM. Dentist has an important role in prevention and treatment and should be part of the oncology team. Before radiation, CT or HSCT dentist should remove sharp teeth edges, polish sharp fillings and crowns, remove orthodontic appliances, do the necessary dental treatment of symptomatic teeth, remove supragingival calculus deposits, treat any oral mucosal lesions, and perform tooth extractions if needed. Although there was insufficient evidence to support the professional oral care for OM prevention, the MASCC/ISOO panel is of the opinion that dental evaluation and treatment as indicated before

cancer therapy are desirable to reduce risk for local and systemic infections from odontogenic source[1]. The dentist is not only important because of dental interventions but is also a key figure in educating the patient about basic oral care procedures to minimize OM and other oral consequences of RT, CT or HSCT. The dentist needs to warn the patient that expected OM is not easy to tolerate, but with preventive and curative methods it will be easier to tolerate and will eventually pass. The dentist also needs to warn the patient that OM is the most difficult side effect of oncology treatment but should not be the cause of interruption or pause in oncology treatment. It is important to emphasize to the patient how the complex oral microflora disrupts normal healing and to educate about oral hygiene procedures including teeth brushing, flossing, and rinsing with a mild solution such as saline or sodium bicarbonate in order to reduce the bacterial load in the oral cavity[9, 17]. It should be noted that the use of interdental brushes and floss is not recommended for patients whose platelet count is less than $40x10^9$ / L due to bleeding[18]. It is recommended to brush teeth and gums with soft brushes, light circular motions, three up to four times a day, preferably after meals and before bedtime. To protect tooth enamel, it is necessary to use non-abrasive toothpaste with a fluoride concentration between 1000 and 1500 ppm and to avoid tooth whitening pastes[17]. In some patients undergoing head and neck radiation therapy, a dentist may recommend a toothpaste with a higher fluoride concentration (above 1500 ppm)[19]. A patient consuming tobacco product should be warned about cessation of smoking because it favors dry mouth and consequent complications and also the recurrence of the underlying disease. When it comes to the use of mouthwashes, those that contain corrigents such as menthol and alcohol should be avoided due to mucosal irritation[18]. According to MASCC/ISOO guidelines, the use of chlorhexidine-based solutions in patients undergoing head and neck radiotherapy for the prevention or treatment of OM is not recommended due to no clear evidence of efficacy. However, it is acceptable to use CHX if an oral infection develops at the same time as OM[1].

Mouthwash containing the non-steroidal anti-rheumatic agent diclofenac also give promising results. The study by Brennan et al.[20] shows a significant reduction in pain in patients with oral mucositis, but further randomized clinical trials are needed for the wider use of this type of rinsing solution. A polyvinyl-pyrolidone-based gel, such as Gelclair, can be used to protect exposed nerve fibers to coat the surface of the oral mucosa, in order to form a thin protective film[21].

BENZYDAMINE

Benzydamine (N, N-dimethyl-3 - [(1-benzyl-1H-indazol-3-yl) ossi] -1-propanamine) is a topical anti-inflammatory drug with analgesic and anesthetic properties. Its activity is similar to nonsteroidal anti-inflammatory drugs. But unlike NSAIDs, benzydamine acts exclusively on local inflammatory factors by suppressing the production of proinflammatory cytokines (TNF-α, IL-1β, and prostaglandins), and also as an antioxidant (removes ROS)[22]. Benzydamine has recently been recommended in new MASCC/ISOO guidelines for OM prevention in patients undergoing a moderate dose head and neck radiotherapy (>50 Gy) (LoE I) and suggested for OM prevention in head and neck patients undergoing radiotherapy with concomitant chemotherapy (LoE II)[1]. Rastogi et al. administered benzydamine to patients receiving doses greater than 50 Gy and were able to significantly reduce the rate of third-degree OM. All of the latter facts may confirm that benzydamine could be one of the most significant agents in the treatment and prevention of OM[23].

PHOTOBIOMODULATION

Photobiomodulation (PBM), also known as low level laser therapy represents the use of lasers or incoherent light sources such as LEDs (Light Emmitting Dioide), which have a beneficial effect on cellular metabolism. The principle of operation is the transfer of photon energy to a specific organelle within the cells, which will consequently lead to changes in metabolism. One of the primary cellular targets of this form of therapy is mitochondria that respond to absorption of red to infrared light by increasing respiratory chain activity to transport electrons resulting in increased

ATP production and less cellular susceptibility to stress-induced apoptosis[24]. In addition, it inhibits the activity of the COX-2 enzyme responsible for the conversion of arachidonic acid to prostaglandine[16], increases the production of pro-collagen and growth factors, and accelerates cell division, which contributes to faster healing[25]. MASCC/ISOO recommends PBM therapy in the prevention of OM in patients undergoing HSCT (LoE I) as well as in patients with head and neck cancer treated only with RT (LoE I) or RT and CT (LoE II). It is important to follow these protocols strictly to optimize clinical efficacy. Each of these protocols is individual to each treatment modality. Further testing is needed to standardize the laser parameters required for optimal performance[1]. Despite the many positive effects of PBM therapy, some studies show that this therapy can have a carcinogenic effect in the long run[26]. However, long-term follow-up studies with conflicting evidence have recently been published[27, 28]. It is therefore advised that the clinician should inform patients about the expected benefits and potential risk of PBM therapy[1]. In addition, for economic reasons, this therapy is not yet available in all healthcare facilities.

CRYOTHERAPY

Cryotherapy or cold therapy results in vasoconstriction of superficial blood vessels thereby limiting the distribution of chemotherapeutics and reducing harmful effects on the oral mucosa. Because cooling is a temporary process, the MASCC/ISOO guidelines recommend cryotherapy in two instances: to prevent the development of oral mucositis in patients undergoing autologous HSCT when conditioning involves a high dose of melphalan chemotherapeutics. Also, 30-minute use of oral cryotherapy is recommended to prevent oral mucositis in patients receiving a 5-fluorouracil (5-FU) bolus. In these instances cases, it is a cytotoxic protocol that is implemented in a short time or cytotoxic agents with a short half-life[1]. This protocol has been shown to be effective with 5-fluorouracil and melphalan, while with other chemotherapeutics such as vinblastine, methotrexate, cisplatin, etoposide, mitomycin and edatrexate, there are no reliable results. When using chemotherapeutics such as oxaliplatin, cryotherapy is contraindicated due to possible neurological side effects such as mandibular stiffness and laryngopharyngeal dysaesthesia[14]. In conclusion, the efficacy of cryotherapy in OM may be limited to chemotherapeutic agents, and there is no evidence that OC would be effective in preventing radiotherapy-induced OM[29].

OPIOID ANALGESICS

Numerous studies speak in favor of locally applied morphine in the treatment and relief of pain in OM[30]. The beneficial effects of topical morphine may not be limited to its analgesic effects. Some evidence confirms that delta-opioid receptors are expressed on epithelial cells of the oral cavity, and morphine can accelerate cell migration, which in turn may aid in the wound healing process. In addition to pain relief, topical morphine therapy has its advantages such as simplicity, low cost, minimal systemic side effects, and better patient compliance[31]. The MASCC/ISOO guidelines suggest the use of 0.2% topical morphine in the form of a mouthwash to relieve OM pain in patients undergoing chemoradiotherapy for oral cancer (LoE III)[1]. OM may adversely affect the absorption of analgesics and thus cause insufficient efficacy. It is therefore necessary to explore alternative ways of administering analgesics to effectively eliminate and control pain. In a study conducted by Mazzola et al., transmucosal preparations of fentanyl (fentanyl pectin nasal spray) have shown excellent results in combating transient exacerbation of pain caused by oral mucositis, allowing patients to consume food normally and complete a planned radiotherapy program. Fentanyl-based preparations are 50 to 100 times more potent than morphine and therefore require extra caution during use[32].

GROWTH FACTORS

Recombinant human keratinocyte growth factor (KGF-1), also known as palifermin, binds to the KGF receptor by stimulating cell growth, proliferation, differentiation, and enhanced regulation of cytoprotective mechanisms. Thus, palifermin can prevent epithelial cell apoptosis and prevent epithelial DNA damage, reduce the number of proinflammatory cytokines, and increase protective enzymes against free radicals[33]. According to the

MASCC/ISOO guidelines, the use of KGF-1 intravenously is recommended in the prevention of OM in patients undergoing autologous HSCT with a conditioning regimen that includes high doses of chemotherapy and total body irradiation (TBI)[1]. In addition to a narrow indication area and a relatively high price, EMA (European Medicines Agency) withdrew palifermin from the market in 2016 at the request of the marketing authorization holder[34]. The drug is still available in the USA[35].

The dentist needs to warn the patient that OM is the most difficult side effect of oncology treatment but should not be the cause of interruption or pause of radiotherapy or chemotherapy treatment. With preventive and curative methods provided by the dentist, OM can be more easily tolerated, and the patient will be able to complete the treatment of the primary disease.

NATURAL REMEDIES AND MISCELLANEOUS AGENTS

New evidence for several natural remedies and herbs has been identified in the MASCC/ISOO guidelines, but there is still not enough evidence to form guidelines. In the prevention of OM in patients on RT or chemo-radiotherapy, topically or systemically applied honey has been suggested as a natural agent[1]. In addition, topically applied turmeric-based gel or turmeric-based mouthwash has shown promising results. Research by Dharman et al speaks in favor of reducing inflammation caused by OM in patients treated with turmeric-based preparations. Turmeric has antioxidant, analgesic, anti-inflammatory and antimicrobial properties that help in faster wound healing against pro-inflammatory cytokines, cyclooxygenase, prostaglandins and is also effective against pro-inflammatory cytokines, cyclooxygenase and prostaglandin E[36]. However, there was no sufficient evidence to form a definitive clinical guideline[1].

THE LATEST INSIGHTS

Recent research has shown that the drug avasopazem manganese (AVA), in addition to protecting healthy tissues from nonselective radiation, also has the ability to make tumor cells more susceptible to radiation. AVA is a mimetic of superoxide dismutase, an enzyme that catalyzes the conversion of a superoxide radical to ordinary molecular oxygen and hydrogen peroxide in the body. In the presence of superoxide, the divalent manganese ion oxidizes to trivalent thereby reducing the superoxide to hydrogen peroxide and molecular oxygen. Because superoxide is associated with the development of OM, avasopazem manganese has great potential in preventing and reducing the clinical picture of OM in cisplatin-treated head and neck cancer patients. Although AVA reduces the impact of radiation on healthy tissues, the effect of stronger action on tumor cells is achieved in combination with stereotactic ablative radiotherapy where high doses of radiation with ablative, high doses of fractions (higher than 7.5 Gy per fraction) are used. This synergy of drug and radiotherapy is currently in a phase III clinical trial conducted in humans[37]. In addition to AVA, nanoencapsulated doxorubicin (DOX) also yields promising results. DOX is a chemotherapeutic that has been linked to the development of mucositis. Combination with nanostructured lipid carriers could reduce drug toxicity to mucosal structures. The results have so far been evaluated only in the mouse intestine area, and an assessment of the efficacy of encapsulated doxorubicin and in the oral cavity could yield more valuable results[38]. The results of Oshvandi et al. show that the use of zinc chloride-based mouthwash can also have a beneficial effect on the oral cavity during radiotherapy. Zinc stimulates cell growth and suppresses apoptosis and, acting as an antioxidant, protects tissue from the action of free radicals that promote the formation of mucositis. Several clinical randomized studies are needed to confirm or refute these results[39].

CONCLUSION

OM is a side effect of oncological treatment that is the most difficult to tolerate and is not only a local problem in the oral cavity, but also a general health problem of patients. Quality care for patients with oral mucositis requires multidisciplinary approach, emphasizing crucial role of dentists

in the oncology team in the prevention and alleviation of mucositis and the consequences of mucositis. Dental preparation for oncology treatment, proper oral hygiene education and oral care in oncology treatment are, in addition to reducing and eliminating pain, among the key factors for relieving symptoms and improving the quality of life of patients with malignancies. None of the therapeutic modalities known today can completely eliminate oral mucositis, but only alleviate the existing condition and prevent secondary infections, but the role of the dentist is indispensable.

Conflicts of interest: Authors declare no conflicts of interest.

REFERENCES

1. Elad S, Fong Cheng KK, Lalla RV, Yarom N, Hong C, Logan RM et al. Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2020;126:4423-31.
2. Bhatt V, Vendrell N, Nau K, Crumb D, Roy V. Implementation of a standardised protocol for prevention and management on oral mucositis in patients undergoing haemopoitiec stem cell transplant. J Oncol Pharm Pract 2010;16:195-204.
3. Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Ann Oncol 2010;21:261-5.
4. Li E, Trovato JE. New developments in the management of oral mucositis in patients with head and neck cancer or receiving targeted anticancer therapies. AM J Health Syst Pharm 2012;69:1031-37.
5. Sultani M, Stringer AM, Bowen JM, Gibson RJ. Anti-inflammatory cytokines: important immunoregulatory factors contributing to chemotherapy-induced gastrointestinal mucositis. Chemother Res Pract [Internet]. 2012;2012. [cited 2022 Feb 11]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437608/.
6. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer 2004;4:277-84.
7. Pulito C, Cristaudo A, Porta C, Zapperi S, Blandino G, Morrone A et al. Oral mucositis: the hidden side of cancer therapy. J Exp Clin Cancer Res 2020;39:210.
8. 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;6:423-31.
9. Vanlancker E, Vanhoecke B, Sieprath T, Bourgeois J, Beterams A, De Moerloose B et al. Oral microbiota reduce wound healing capacity of epithelial monolayers, irrespective of the presence of 5-fluorouracil. Exp Biol Med 2018;243:350-60.
10. Treister N, Sonis S. Mucositis: biology and management. Curr Opin Otolaryngol Head Neck Surg 2007;15:123-9.
11. Logan RM, Stringer AM, Bowen JM, Yeoh ASJ, Gibson RJ, Sonis ST et al. The role of pro-inflammatory cytokines in cancer treatment-induced alimentary tract mucositis: pathobiology, animal models and cytotoxic drugs. Cancer Treat Rev 2007;33:448-60.
12. Brailo V, Boras VV, Juras DV, Rogulj A, Brzak BL, Alajbeg I. Oral Side Effects of Head and Neck Irradiation. *In*: Akarslan Z (ed). Diagnosis and Management of Head and Neck Cancer. London: IntechOpen [Internet]. 2017;168. [cited 2022 May 24]. Available from: https://www.intechopen.com/chapters/55403.
13. Kostler WJ, Hejna M, Wenzel C, Zielinski CC. Oral Mucositis Complicating Chemotherapy and/or Radiotherapy: Options for Prevention and Treatment. CA Cancer J Clin 2001;51:290-315.
14. Chaveli-López B, Bagán-Sebastián JV. Treatment of oral mucositis due to chemotherapy. J Clin Exp Dent 2016;8:201-9.
15. Valeh M, Kargar M, Mansouri A, Kamranzadeh H, Gholami K, Heidari K et al. Factors Affecting the Incidence and Severity of Oral Mucositis Following Hematopoietic Stem Cell Transplantation. Int J Hematol Oncol Stem Cell Res 2018;12:142-52.
16. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent Clin North Am 2008;52:61-8.
17. Peterson DE, Srivastava R, Lalla RV. Oral mucosal injury in oncology patients: perspectives on maturation of a field. Oral Dis 2015;21:133-41.
18. Oral cancer foundation [Internet]. New Port Beach: Mucositis, c2022 [cited 2022 Apr 20]. Available from: https://oralcancerfoundation.org/complications/mucositis/.
19. Woking & Sam Beare Hospices [Internet]. Woking: European Oral Care in Cancer Group – Oral Care Guidance and Support, c2022 [cited 2022 May 24]. Available from: https://www.wsbhospices.co.uk/wp-content/uploads/2017/12/EOCC-Guidelines-online-version-v8.pdf.
20. Brennan PA, Lewthwaite R, Sakthithasan P, McGuigan S, Donnelly O, Alam P et al. Diclofenac Mouthwash as a potential therapy for reducing pain and discomfort in chemo-radiotherapy-induced oral mucositis. J Oral Pathol Med 2020;49:956-59.
21. Smith T. Gelclair: managing the symptoms of oral mucositis. Hosp Med 2001;62:623-6.
22. Nicolatou-Galitis O, Bossi P, Orlandi E, Bensadoun RJ. The role of benzydamine in prevention and treatment of chemoradiotherapy-induced mucositis. Support Care Cancer 2021;29:5701-9.
23. Rastogi M, Khurana R, Revannasiddaiah S, Jaiswal I, Nanda SS, Gupta P et al. 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;25:1439-43.
24. Cronshaw M, Parker S, Anagnostaki E, Mylona V, Lynch E, Grootveld M. Photobiomodulation and Oral Mucositis: A Systematic Review. Dent J 2020;8:87.
25. Lopes NN, Plapler H, Lalla RV, Chavantes MC, Yoshimura EM, Bastos da Silva MA et al. Effects of low-level laser therapy on collagen expression and neutrophil infiltrate in 5-fluorouracil-induced oral mucositis in hamsters. Lasers Surg Med 2010;42:546-52.

26. Sonis ST, Hashemi S, Epstein JB, Nair RG, Raber-Durlacher JE. Could the biological robustness of low level laser therapy (photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. Oral Oncol 2016;54:7-14.
27. Antunes HS, Herchenhorn D, Small IA, Araújo CMM, Viégas CMP, de Assis Ramos G et al. Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol 2017;71:11-5.
28. Brandão TB, Morais-Faria K, Ribeiro ACP, Rivera C, Salvajoli JV, Lopes MA et al. Locally advanced oral squamous cell carcinoma patients treated with photobiomodulation for prevention of oral mucositis: retrospective outcomes and safety analyses. Support Care Cancer 2018;26:2417-42.
29. Al-Rudayni AHM, Gopinath D, Maharajan MK, Veettil SK, Menon RK. Efficacy of Oral Cryotherapy in the Prevention of Oral Mucositis Associated with Cancer Chemotherapy: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Curr Oncol 2021;28:2852-67.
30. Cerchietti LC, Navigante AH, Bonomi MR, Zaderajko MA, Menéndez PR, Pogany CE et al. Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. Cancer 2002;95:2230-6.
31. Charbaji N, Schäfer-Korting M, Küchler S. Morphine stimulates cell migration of oral epithelial cells by delta-opioid receptor activation. PLoS One [Internet]. 2012;7. [cited 2022 Apr 20]. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0042616.
32. Mazzola R, Ricchetti F, Fiorentino A, Giaj-Levra N, Fersino S, Tebano U et al. Fentanyl pectin nasal spray for painful mucositis in head and neck cancers during intensity-modulated radiation therapy with or without chemotherapy. Clin Transl Oncol 2017;19:593-98.
33. Blijlevens N, Sonis S. Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis. Ann Oncol 2007;18:817-26.
34. European Medicines Agency [Internet]. Amsterdam: Kepivance, withdrawal of the marketing authorisation in the European Union, c2022 [cited 2021 Oct 24]. Available from: https://www.ema.europa.eu/en/documents/public-statement/public-statement-kepivance-withdrawal-marketing-authorisation-european-union_en.pdf.
35. Food and Drug Administrarion [Internet]. Maryland: Palifermin (marketed as Kepivance) Food and Drug Administration. [citated 2022 May 24]. Availabe from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/palifermin-marketed-kepivance.
36. Dharman S, Maragathavalli G, Shanmugasundaram K, Sampath RK. A Systematic Review and Meta-Analysis on the Efficacy of Curcumin/Turmeric for the Prevention and Amelioration of Radiotherapy/Radiochemotherapy Induced Oral Mucositis in Head and Neck Cancer Patients. Asian Pac J Cancer Prev 2021;22:1671-84.
37. Sonis ST. Superoxide Dismutase as an Intervention for Radiation Therapy-Associated Toxicities: Review and Profile of Avasopasem Manganese as a Treatment Option for Radiation-Induced Mucositis. Drug Des Devel Ther 2021;15:1021-29.
38. Pinto CM, Horta LS, Soares AP, Carvalho BA, Ferreira E, Lages EB et al. Nanoencapsulated Doxorubicin Prevents Mucositis Development in Mice. Pharmaceutics 2021;13:1021.
39. Oshvandi K, Vafaei SY, Kamallan SR, Khazaei S, Ranjbar H, Mohammadi F. Effectiveness of zinc chloride mouthwashes on oral mucositis and weight of patients with cancer undergoing chemotherapy. BMC Oral Health 2021;21:364.
40. Finocchiaro G. Actinomycin D: a new opening for an old drug. Neuro Oncol 2020;22;1235-36.
41. Hsin-Chieh W, Domitille R, Berthier C, Hleihel R, Sakamoto T, Quentin S et al. Actinomycin D Targets NPM1c-Primed Mitochondria to Restore PML-Driven Senescence in AML Therapy. Cancer Discov 2021;11:3198-13.
42. Mediately [Internet]. Ljubljanja: Cisplatin. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/Ae3yqTFQyOJGO78nGbPzurepXDs/cisplatin-pfizer-1-mg-ml-koncentrat-za-otopinu-za-infuziju.
43. Mediately [Internet]. Ljubljanja: Docetaxel. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/1QOYYW2sQGH22TKQLQKO06Etqoh/docetaxel-accord-160-mg-8-ml-koncentrat-za-otopinu-za-infuziju.
44. Mediately [Internet]. Ljubljanja: 5-Fluorouracil. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/TgxNI8aJvffPM2hBZUKPUYEA1gF/fluorouracil-pliva-50-mg-ml-otopina-za-injekciju-infuziju.
45. Misra DP, Gasparyan AY, Zimba O. Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: searching for repurposable drug candidates. Rheumatol Int 2020;40:1741-51.
46. Larsen RH, Hjalgrim LL, Degn M, Nersting J, Als-Nielsen B, Grell K et al. Dynamics of leucocyte DNA thioguanine nucleotide levels during maintenance therapy of childhood acute lymphoblastic leukemia. Cancer Chemother Pharmacol 2021;88:53-60.
47. Mediately [Internet]. Ljubljanja: Amsakrin. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/Q1jBfeRtH2cfaXof80Wpu0J0Foo/amlyo-75-mg-prasak-za-koncentrat-za-otopinu-za-infuziju.
48. Mediately [Internet]. Ljubljanja: Doxorubicin. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/5AwUAlOQdfRHhHqQoA3jJPysip2/doxorubicin-pliva-2-mg-ml-otopina-za-injekciju-infuziju.
49. Mediately [Internet]. Ljubljanja: Etoposide. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/GZwWLJjYwHI0az60lxbC5hc2WVq/etoposide-sandoz-20-mg-ml-koncentrat-za-otopinu-za-infuziju.
50. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases- Mitoxantrone. [cited 2022 Apr 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547931/.
51. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases- Bleomycin. [cited 2022 Apr 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548499/.

52. Mediately [Internet]. Ljubljanja: Citarabin. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/LsOjMxJf71ac16CKA4B9HbYta46/cytosar-1-g-prasak-za-otopinu-za-injekciju-infuziju.

53. Mediately [Internet]. Ljubljanja: Daunorubicinklorid. [cited 2022 Apr 20]. Available from: https://mediately.co/hr/drugs/7pzHWjClj1dqmMl7xLfGNMkouhx/daunoblastina-2-mg-ml-prasak-i-otapalo-za-otopinu-za-injekciju.

54. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases-Floxuridine. [cited 2022 Apr]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548421/.

55. Islam B, Lustberg M, Staff NP, Kolb N, Alberti P, Argyriou AA. Vinca alkaloids, thalidomide and eribulin-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst 2019;24:63-73.