Review paper

Procedure in the prevention and nurturing of inflammatory changes of oral mucositis among patients treated for oncological conditions

Postępowanie w profilaktyce i pielęgnowaniu zmian zapalnych błony śluzowej jamy ustnej u pacjentów leczonych onkologicznie

Marzena Kamińska, Magdalena Juszkiewicz, Renata Tymicka, Agnieszka Bronikowska, Agnieszka Kolak

Clinical Oncology Ward, St. John's Cancer Centre, Lublin, Poland
Head of Centre: Prof. Elżbieta Starosławska MD, PhD

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Abstract

Oral mucositis is a serious complication occurring in the process of chemotherapy and/or radiotherapy. Ailments related to oral mucositis may bring about pain, reduce the amount of food intake, and eventually deteriorate the quality of life. This complication arises after radiotherapy, chemotherapy, transplantation of haematopoietic stem cells, and after molecularly targeted therapy. These symptoms may be the result of delay of treatment or dose reduction of successive cycles of chemotherapy, which, consequently, may have an impact on oncological treatment.

Streszczenie

Zapalenie błon śluzowych jamy ustnej jest poważnym powikłaniem towarzyszącym chemioterapii i/lub radioterapii. Dolegliwości związane z przebiegiem zapalenia błon śluzowych jamy ustnej mogą powodować ból, ograniczać spożywanie pokarmów i ostatecznie pogarszać jakość życia chorych. Powikłanie to występuje po zastosowaniu radioterapii, chemioterapii, przeszczepieniu macierzystych komórek krwiotwórczych oraz leczeniu ukierunkowanym molekularnie. Objawy te mogą być przyczyną opóźnienia leczenia lub redukcji dawek kolejnych cykli chemioterapii, co w konsekwencji może rzutować na wyniki leczenia onkologicznego. Niezwykle istotne jest opracowanie zasad oceny stanu jamy ustnej i postępowania profilaktyczno-leczniczego, w tym instruktażu utrzymania higieny w jamie ustnej. Dokładne monitorowanie przebiegu całego leczenia i ukierunkowana edukacja może znacznie ograniczyć występowanie objawów niepożądanych.

Properly balanced diet involves providing essential nutrient elements, which influence health and life of patients suffering from tumour disease. Nutrition plays a crucial role in maintaining good body condition that enables effective treatment to be conducted [1].

Mucositis – described as mucosal barrier injury (MBI), located in the oral cavity – described as oral MBI (OMBI), and located in further parts of alimentary canal – described as gut MBI (GMBI), is a result of oncological chemotherapy.

From the patient's point of view oral mucositis is a frequent and the most severe complication occurring during anti-cancer treatment. This complication arises after radiotherapy, chemotherapy, and transplantation of haematopoietic stem cells, as well as after molecularly targeted therapy.

The frequency of MBI is as follow: 85–100% among patients underlying radiotherapy in head and neck, 75–100% among patients after marrow transplantation, and 5–40% among patients treated for solid tumours [2].

Oral mucosa, due to the high frequency of cell divisions, is particularly sensitive to the toxic effect of cytostatic agents and X-rays [3].

Oral mucositis may develop along with infection or may be a result of non-infectious factors, such as the toxic effect of some cytostatic agents on mucosa and/or radiotherapy as well as graft vs. host disease (GvHD) [4].

Oral mucositis may appear as inflammation, erosions along with inflammation, ulcerations, or bleeding. Changes usually occur in non-keratinised oral mucosa of cheeks, lips, floor of the mouth, lateral and bottom surface of tongue, and soft palace [5]. There is

often pain in the oral cavity that hinders chewing and taking in food administered orally, taste disorders, and deterioration of quality of life [6].

Water-electrolyte balance disorders, calorie deficiency, and inflammations spread through damaged mucosa, mainly bacterial and fungal, may arise as a consequence of these ailments. They may pose a direct threat to the patient's life as co-existing immunological deficiencies foster infection development.

The frequency and severity of changes in the oral cavity depend on the type of tumour disease as well as the length and intensity of chemical treatment [2]. The most damaging cytostatic agents include antimetabolic agents, such as: methotrexate, 5-fluorouracil, and cytostatic antibiotics: bleomycin and mitomycin C [7].

Other factors influencing damage and inflammatory changes in oral cavity include: age, sex, and the patient's nutritional state. Conducted research proves that symptoms related to oral mucositis occur more often among women, and in younger and older patients (over 65-year-old). An additional risk factor may be low body mass index (BMI) and the presence of neutropaenia [8].

Pathological changes are observed a few days after introduction of oncological treatment. Not only does MBI influence deterioration of the patient's quality of life, but it also impairs the patient's life functions related to securing the elementary health needs (nutrient needs), and hinders and often disenables the conduction of the oncological treatment program since it generates high costs [9].

There is often pain in the oral cavity that hinders chewing and taking in food administered orally, taste disorders, and deterioration of quality of life [6].

It has been proven that they can be connected with the applied treatment plan and the time of administering drugs, as well as patient's general state [10]. According to some authors, around 1/3 of systemic infections occurring in neutropaenia stem in the oral cavity [11, 12].

Complication in form of oral mucositis is a complex process that compromises four phases: inflammatory, epithelial, ulcerative-bacterial, and healing [13].

Inflammatory changes in the oral cavity may result from hindering the division of stem cells, damaging epithelial stem cells as a result of cytostatic drugs, and irradiation, which leads to pathological epithelium differentiation that rebuilds during a 7–14-day period. Inflammatory changes may also occur as a result of injuries and following the disappearance of mucosa, lowered protein level due to cachexia, dehydration, alcohol consumption, or smoking, as well as improper oral hygiene. Symptoms occurring during treatment in the form of leukopaenia increase the risk of developing an infection caused by fungi, bacteria, and physiological saprophytic viruses. On the other hand, a level of blood platelets lower than 40×10^9/l leads to bleeding [14, 15].

The severity of oral mucositis varies. It is described by the four-stage scale according to World Health Organisation (WHO):
- I° – redness and oedema of mucosa, feeling of discomfort in the oral cavity,
- II° – redness, oedema, and erosions on oral mucosa; patient may consume solid food,
- III° – oral mucositis, ulcerations; patient takes in fluids and cannot consume solid food,
- IV° – inflammatory and necrotic changes, deep and vast; they not only embrace the oral cavity but also the lips, throat, and oesophagus; patient cannot take in any fluids or solid food and is on parenteral nutrition [16].

In order to facilitate the evaluation of oral mucosa the National Cancer Institute (NCI) has developed an objective and easy-to-use evaluation scale called Terminology of Common Terminology Criteria for Adverse Events (CTCAE) [17].

It is a five-stage scale from 0 to 4, where 0 means no changes, 1 means painless ulcerations and redness, 2 means painful redness and ulcerations, 3 means painful redness and ulcerations in connection to hindered swallowing due to pain, and 4 means vast ulcerations which may require intubation. In the five-stage scale the effectiveness of swallowing reflex is also assessed. A value of 0 means no difficulties with swallowing; 1 – pain while swallowing, but intake of solid food is possible; 2 – patient requires semi-liquid or liquid diet; 3 – patient also requires drip insertion; and 4 – patient cannot swallow.

The National Cancer Institute also recommends using a questionnaire of pain valuation scale in order to assess the state of oral mucosa. Thanks to this, it is possible to assess subjectively the severity of pain felt by the patient [17].

Infections of the oral cavity may occur, such as candidiasis caused by *Candidia albicans*. It is the most frequent fungal infection resulting in pain, redness, swelling, and dryness of oral mucosa. After 2–3 days white plaques may appear, looking like cottage cheese. Removing them may reveal surface erosions, burning, and a strong metallic taste.

Angular cheilitis is also commonly diagnosed. It is characterised by redness, dryness, and painful cracking. There are no infiltration and scrubs [18].

Herpes caused by herpes simplex virus type 1 or 2 (HSV1 and HSV2) may lead to oral cavity infection. Changes induced by this type of virus are pictured as painful itchy blisters occurring at the end of oral mucosa and mucous membrane of the lips. Primarily, the blisters are filled with serous fluid, then with pus, and within a few days they are covered with scrubs.

Infections caused by Gram-positive bacteria, mainly by staphylococci and streptococci, appear

in the form of dry, elevated, yellow-brownish, wart-alike, round plaques;

Infections are caused by Gram-negative bacteria, appearing in the form of cream-whitish, slightly embossed, shiny, non-purulent erosions on a reddish surface.

The severity of pain depends on the level of damage of mucosa. Pain sensations may cause a reduction in taking in food and deteriorate quality of life, which leads to weakening collaboration with patient. Pain also limits verbal and non-verbal communication, resulting in depression and sleep disorders. Severe inflammation of the mucous membranes with vast ulcerations increases the risk of malnutrition and cachexia, often requiring parenteral feeding and administration of painkillers. It has been shown that 55% of patients may lose 10% or more of body weight during radiotherapy or chemotherapy due to their toxicity [19].

One of the most essential elements of total care of the patient should be preventative efforts, which may have an impact on decreasing the risk of intense pH value of oral mucosa and its complications [20].

These efforts should be made before chemotherapy or radiotherapy. What is also important is dental consultation, and accurate oral cavity cure including treatment or removal of decayed teeth, treatment of periodontal diseases, and scaling and treatment of all potential sources of infection. If removal of teeth is required, it should be conducted a minimum of 2 weeks prior to treatment. Orthodontic treatment should also be ceased in the period of oncological treatment. A dentist and dental hygienist should be a part of a group that will permanently take care of oncological patients [21].

The role of targeted education of patients in terms of maintaining oral hygiene as an essential element of anti-cancer treatment should be emphasised. What is also crucial is the influence of the immediate environment on awareness and health activity. Self-service dexterity and the loss of health competences are often lowered in the process of treatment. Favorable health behaviors of patient and their close family and friends influence intensification of symptoms related to oncological treatment, including with MBI.

Good motivation shown by the patient, as well as scrupulous following of the hygiene regime, significantly reduces oral cavity complications.

Regular nursing of the alimentary tract including own dentition and dental prosthesis, oral mucosa, tongue, and throat helps to maintain optimal ecosystem conditions of the oral cavity during tumour disease. Irregular nursing of dental prostheses leads to re-infections.

Individual and elementary recommendations for the patient should include regular (three times a day) evaluation of oral mucosa in good light, where tongue should be slid off and any prosthesis taken out. The duration of mucositis after chemotherapy varies. Borgmann *et al.* [22] defined the average duration of mucositis after chemotherapy as eight days, whereas Borowski *et al.* [23] described it as 11 days, in spite of maintaining proper oral hygiene.

If there is no secondary infection, the inflammation goes away by itself within 4 weeks of the last dose of cytostatic agent. In case of irradiation of tumours of the head and neck this complication is the most intensified in 4–6 weeks after treatment and usually lasts for a few weeks after radiotherapy [24].

Preventive efforts should include regular hygiene of oral cavity, throat, and teeth 30 min after a meal and every four hours during wakefulness. The tooth brush should be soft, made from nylon bristles, and it should be changed regularly. It should also be scalded in hot water before each usage and stored in a dry place. It is recommended to use a delicate toothpaste with flour or a paste made from baking soda and water that does not contain any abrasive components. It is necessary to pay attention to brushing and cleaning the spaces between the teeth using dental floss. It should be avoided in cases of thrombocytopaenia or gum bleeding (it is allowed if the level of thrombocytes is higher than 40,000/mm^3 and the level of leukocytes is higher than 1500/mm^3).

It is recommended to frequently rinse the oral cavity using solutions in order to maintain proper moisture and hygiene of oral mucosa: hydrogen peroxide with boiled water (1 : 4) or hydrogen peroxide with physiological saline (1 : 2); however, the hydrogen peroxide solution should be prepared directly before usage and the mouth should be rinsed for 1–1.5 min with salt (1/2 tea spoon) mixed with soda (1 tea spoon) and boiled water (1 l). Vitamin mixtures are also recommended (Vitamin B complex, vitamin PP, and vitamin C), electrolyte solutions Caphosol® – a saturated solution of calcium and phosphate ions used to rinse the oral cavity 4–6 times a day, washes containing LP3 meaning lacto peroxidase, lactoferrin, and lysozyme (Biatene™), and herbal brews with anti-inflammatory and astringent effects (salvia, oak bark, chamomile, and mallow).

The most common rinsing solutions include: 0.2% chlorhexidine solution [25, 26] or mixed with nystatin [25], iodine solution [27], 0.05% sodium fluoride solution [28], and chamomile infusion [29].

Cryotherapy (cooling the oral cavity) is also recommended, and sucking crushed ice cubes for 30 min by patients receiving bolus 5-fluorouracil 5 min before infusing cytostatic agent. Cooling the oral cavity during infusion of 5-FU and while receiving high-dose chemotherapy may reduce (by half) the frequency of vesicular stomatitis caused by cytostatic agents.

It is also possible to apply local anaesthetic agents, the effect of which is exclusively ad-hoc, such as lidocaine or benzocaine gel. There are also solid gels

with hyaluronic acid available that may alleviate the symptoms. Applying locally on denture gels and varnishes containing high concentrations of fluoride compounds, especially during the ulcerative phase, is favourable, and it does not cause ailments.

The efficiency of palifermin, keratinocyte growth factor human (KGF) developed by means of recombinant DNA by bacteria Escherichia coli, has also been proven to prevent oral mucositis in cases of applying high-dose chemotherapy or radiotherapy [30].

According to ESPEND recommendations, digestive tract feeding is favoured among patients if their health condition allows it [31].

There are also washes, gels, varnishes, toothpastes, and chewable tablets containing chlorhexidine (CHX) applied due to its favorable bactericide effect to prevent OM. Chlorhexidine also shows bactericidal activity against anaerobic microorganisms, which belong to the flora of the ecosystem in the oral cavity [32].

Formulations with chlorhexidine, including varnishes, block adhesion of microorganisms to mucous membrane showing anti-inflammation activity and hindering creation and aggregation of dental plaque to dental tissues showing cariostatic action. The frequency of applying formulations is adjusted to the health needs of the patient at that time [33].

Research carried out by Cheng *et al.* regarding recommendation of chlorhexidine formulations has shown that maintaining a high level of hygiene in the oral cavity combined with application of 0.2% chlorhexidine solution allows a reduction of 38% in the number of OM cases among patients having chemotherapy [34].

Due to its irritancy it is not recommended to apply chlorhexidine agents containing alcohol [14, 35, 36].

It is necessary to follow dietary recommendations to prevent conditions related to oral mucositis. It includes a high-protein and high-vitamin diet, avoiding irritating, sour, spicy, or salty meals as well as rough, tough, and dry food. It is also recommended to eat frequently but in small portions.

What is also essential is maintaining proper food temperature (ideally about 25°C), which is aimed at eliminating thermal injury of the patient's mucosa [1].

Vegetables and fruit should not be excluded from the diet during the treatment due to microelements, vitamins, polyphenols, and valuable fibre. A dietician, along with the treating team, should determine whether the patient should eat raw vegetables and fruit or whether they should be exposed to short heat treatment, as well as outline what kind of food preparation should be applied in order to ensure the most favourable digestion, taking into account the presence of GMBI. Food prepared from vegetables and fruit in the form of mash, mush, or puree minimises the possibility of mechanical damage of oral mucosa, and thus does not lead to further development of pathological changes. In contrast, it complements valuable nutrients, diversifies the patient's diet, and stimulates the taste buds.

It is crucial to take in about 3000 ml of liquids daily (unless it is contraindicated). Moreover, in the case of experiencing extreme dryness in the oral cavity it is favoured to: suck sugar-free drops, chew sugar-free gum, dampen dry food with sauces, bitter, and broths, or use saliva substitute products.

It is of a high importance to be supported by staff that directly take care of the patient during oncological treatment. Good mental health of patients battling side effects of oncological treatment greatly depends upon the quality of the support given. This support should embrace all areas of health competencies even if they are damaged. It should be based on information exchange regarding different situations and remedial actions, passing on specific tips regarding actions in case side effects occur, maintaining proper hygiene and controlling emotions that help the patient to hold on and stay calm.

Careful monitoring of the course of treatment may significantly reduce the incidence of undesirable effects. Therefore, taking care of the oral cavity in oncological patients as well as reacting to changes in the oral cavity determine the administration of optimal treatment.

Making the patient aware of their role in minimising the side effects related to oral mucositis shortens recovery time, reduces psychological discomfort, and improves quality of life.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Marzena Kamińska MD
Chemotherapy Word
St. John's Cancer Center
ul. Jaczewskiego 7, 20-090 Lublin, Poland
Phone: +48 607 234 462
E-mail: mkaminska0@vp.pl