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Review/Praca poglądowa

Oral mucositis in patients with leukaemia following high-dose chemotherapy and autologous haematopoietic stem cells transplantation

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ABSTRACT

Historically, oral mucositis (OM) has been identified as a symptom developing in patients undergoing irradiation due to head and neck cancers, those undergoing therapy in preparation for a stem cell transplant, or receiving special therapeutic protocols due to acute myeloid leukaemia. It results from direct toxic injury to the mucosal epithelial cells by the immunosuppressive regimen. In this article we want to describe pathogenesis, diagnostic and actual possibility of treatment of OM. The literature reports several rating scale for OM that have been used for patients undergoing cancer therapy. The most useful of them are Oral Toxicity Scale and Oral Mucositis Assessment Scale. In the prevention and treatment of OM associated with standard chemotherapy various drugs and agents acting locally and systemically are used. Many of them are still remaining in the course of research.

Introduction

Haematopoietic stem cell transplantation (HSCT) involves the intravenous infusion of allogeneic or autologous stem cells collected from bone marrow, peripheral blood or umbilical cord blood in patients whose bone marrow or immune system has been damaged. After administered them into the body, their objective is to re-establish haematopoietic function. In allogeneic transplant, a donor of the same species is the source of cells, and in autologous transplant, haematopoietic cells come from the recipient himself or herself. There are also syngeneic transplants (genetically identical twins). Indications for this therapeutic treatment include primarily haematopoietic malignancies, such as leukaemias, lymphomas, myelomas, myelodysplastic syndromes, advanced lung, ovarian, breast, testicular cancers, as well as benign diseases, such as aplastic

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Table I – Conditioning regimens in PBSCT

BEAM	BCNU, etoposide, cytarabine, melphalan
BuMel	Busulfan, melphalan in high doses
BorMel	Botezomib, melphalan in high doses
Melphalan	High doses 140–200 mg/m^2

anaemia. Conditioning treatment is required in a patient prior to the HSCT, which involves administering high-dose chemotherapy, often in combination with radiation therapy. Such therapy leads to myeloablation and destruction not only of cancer cells, but also of recipient's haematopoietic system. Non-myeloablative transplants with reduced-intensity conditioning are also used, which involve the application of lower doses of chemotherapy in combination with strong immunosuppressive treatment. Such therapy can be used in older patients over 65 years of age on account of lower toxicity. Negative effects of toxic conditioning therapy include intensified inflammations of the mucous membrane of the mouth, nasopharynx and intestines, so called mucositis [1, 2]. Some groups of anticancer drugs which are used alone or in combination, as chemotherapy before autologous HSCT are particularly often responsible for mucositis. The most recorded mucotoxic agents are: thymidine synthetase inhibitors, such as methotrexate, topoisomerase II inhibitors (etoposide, irinotecan); pyrmidine analogues (cytarabine); purine analogues (6-mercaptopurine and 6-thioguanine); alkylating agents at high doses (busulfan, melphalan and cyclophosphamide); and intercalating drugs (idarubicin, doxorubicin, daunorubicin). When these agents are administered in multiple cycles the risk of mucositis increases at each course [3] (Tables I and II).

Pathomechanism and clinical symptoms of mucositis

Inflammation of the mucous membrane lining the oral cavity and other parts of the gastrointestinal tract and nasopharynx is a serious complication of the above mentioned conditioning therapy, and affects 80–100% of patients [4]. The course is often so severe that patients require strong analgesics and parenteral nutrition [5]. In view of patients' subjective opinions, it is also one of the most intolerable side effects of the therapy. It is a pathological process common for cancer patients receiving radiation therapy, chemotherapy or both of these treatments, and patients requiring autogenic stem cell transplantation. Mucosal injuries affect the entire gastrointestinal tract, from oral cavity to anus [6]. Resulting lesions occurring in epithelium and tunica submucosa are characterised in five clinical phases: (a) initiation, (b) primary damage response, (c) signal amplification, (d) ulceration, and (e) healing [7–10] (Tab. III).

Table II – Groups of anticancer drugs responsible for mucositis

Thymidine synthetase inhibitors	Methotrexate
Topoisomerase II inhibitors	Etoposide
Pyrmidine analogues	Cytarabine
Purine analogues	6-Mercaptopurine, 6-thioguanine
Intercalating drugs	Idarubicin, doxorubicin, daunorubicin

Primary mucosal cell injuries resulting from oxidative stress lead to the expression of early response genes and activation of DNA transcription factor. The pathophysiology of mucositis involves various factors, such as nuclear factor kappa B (NF-kappa B) protein complex playing an essential role in the immune response to an infectious agent, cyclooxygenase-2 (COX-2) activated by agents related to the inflammation, pro-inflammatory cytokines – in particular interleukin (IL)-1b (IL)-6, and tumour necrosis factor (TNF) [7, 8]. Clinically, it begins with non-specific oral discomfort preceded by redness, burning sensation, increased sensitivity to sour and hot foods, then erosion and ulcers occur that make it difficult to take and swallow foods, accompanied by a series of other symptoms that make patient's functioning difficult, of which the following should be listed: pain, swelling, fever, mycosis, bacteraemia and sepsis [4, 6, 11, 12]. Then, viral infection symptoms dominate with increased mucosal temperature on hard palate, gingive and dorsum of tongue combined with necrosis and extensive lichenoid lesions. Quantitative and qualitative salivary changes leading to a decrease in salivary IgG, IgA, IgM levels and to xerostomia add to it [6, 9, 12, 13]. As a consequence

Table III – The pathobiology of mucositis-five phases

Phase I	Phase II	Phase III	Phase IV	Phase V
Initiation DNA and non DNA damage	Primary damage response Activation of transcription factors such as NF-kappa B	Signal amplification Positive feedback loops increase cytokine production	Ulceration Bacteria colonise ulcer surface	Healing Migration and proliferation of regenerative epithelial cells
Reactive oxygen species damage basal epithelial cells	Increased production of TNF-α, IL-1, IL-2, IL-6	Clinically minimal signs and symptoms	Increase the activity of macrophages and production of additional proinflammatory cytokines	Mucosa appears clinically normal
Clinically observed tissue destruction	Activation of sphingomyelinase and ceramide Apoptosis of basal epithelial cells and mucosal damage		Clinically evident erosions	

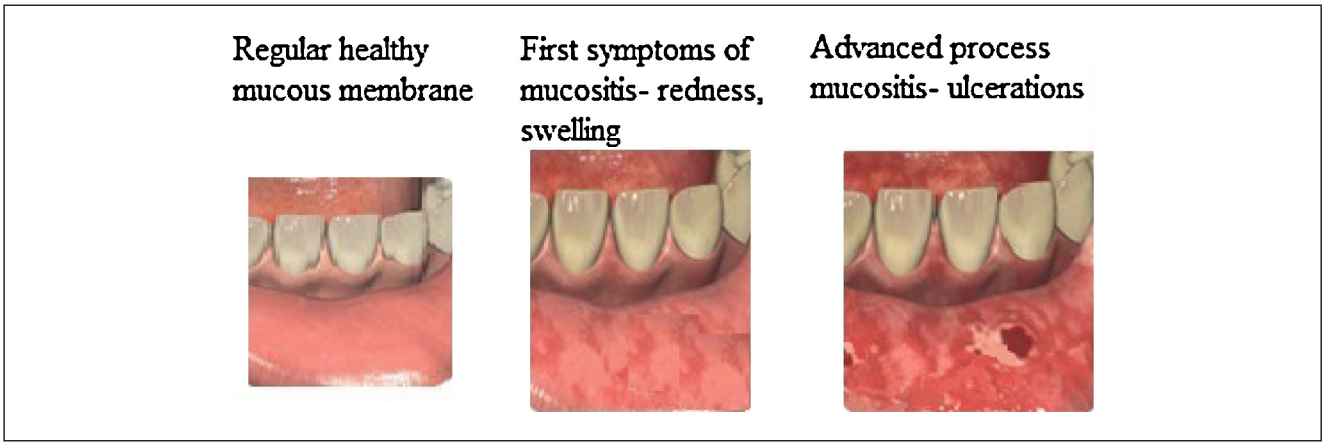

Fig. 1 – Clinical symptoms of mucositis

of the above lesions, microbes appear in the oral cavity which are not present in normal flora in this area, e.g. Gram-negative – *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, Gram-positive: *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguis*, capnophyles and fusobacteria, fungi of the genus *Candida* – *Candida albicans* and *Candida tropicalis*, leading to multi-organ systemic mycosis [12, 13]. Bacterial cell walls produce lipopolysaccharides which stimulate macrophages to produce damaging cytokines (Fig. 1).

Diagnosis and estimate of changes

For the evaluation of OM, two scales to assess lesions within the mucosa are used that have been developed by the World Health Organisation: Oral Toxicity Scale and Oral Mucositis Assessment Scale (OMAS). As regards the interpretation of symbols applied in these scales, 0 represents no pathologic lesions, 1 – erythema requiring no clinical treatment, 2 – presence of pain requiring no analgesics and difficulty in swallowing. In grade 3 – mucosal ulcers, pain requiring painkillers (analgesics) are present, feeding is totally impossible, and finally grade 4 – necrosis and necessity of parenteral nutrition. For more detailed evaluation of lesions in a form of erythema and ulceration, OMAS scale is used: a severity of ulcerations is characterised by 3 groups. This evaluation relates to vermilion on the right and on the left, lip mucosa, jugal mucosa, palate, floor of the mouth, lateral tongue surface on both sides, and dorsal surface of the tongue (Tables IV and V).

The incidence and clinical severity of OM depend on a type and a dose of irradiation, combination of radiation therapy with the chemotherapy, a type and dose of a chemotherapeutic. In the last case, high toxicity of preparations such as 5-FU, cisplatin, etoposide, melphalan was reported, and slightly lower toxicity in the case of drugs such as: doxorubicin, vinblastine, taxan, methotrexate, and finally very rare toxicity if asparaginase and carmustine were administered [8, 9]. Combination therapy with several chemotherapeutics increases the incidence of OM from 40% to 70% compared to standard chemotherapy. In those patients who receive conditioning treatment prior to the HSCT – in particular if it consists of TBI (ionising irradiation – total body irradiation) in combination with chemotherapy – the incidence of OM is 75–99% [9]. Other factors that are not associated with a type of therapy also play a role in etiopathogenesis, namely patient's age, gender, race, general condition, systemic disease. The results from studies carried out to investigate risk factors are inconclusive; however, they suggest that oral inflammation affects more women than men. People over the age of 50 years and children are at higher risk of OM [9]. OM is more common in older people due to the decreased effectiveness of regenerative and immune system processes, and in children due to a greater rate of basal epithelium cells' division [8, 9, 14].

Table IV – WHO's Oral Toxicity Scale

Oral Toxicity Scale	
Grade 1	Soreness ± erythema
Grade 2	Erythema, ulcers; patient can swallow solid food
Grade 3	Ulcers with extensive erythema patient cannot swallow food
Grade 4	Mucositis to the extent alimentation is not possible

Table V – OMAS Oral Assessment Scale in mucositis

Oral Mucositis Assessment Scale (OMAS)	
Erythema	
0°	No erythema
1°	Mild to moderate erythema
2°	Severe erythema
Ulceration	
0°	No clinical lesion
1°	An ulcer $<1\ cm^2$
2°	An ulcer of 1–3 cm^2
3°	An ulcer $>3\ cm^2$

Therapeutic procedure

Apart from the general medical approach, dental management is also an important aspect of comprehensive preparation of a patient both for auto- and allo-HSCT. It should be carried out at least two months prior to the planned transplant, and should include detailed intra- and extra-oral examinations supported by examinations such as an Orthopantomogram (OPG), X-rays of individual teeth of which the state raises doubts, or an X-ray of the paranasal sinuses. Not only teeth should be evaluated, but also oral mucosa, parodontium, parotid glands and their orifices, namely all measures should be taken to identify and eliminate potential foci of infection, and consequently, complications after the transplant. All therapeutic procedures should be carried out in consultation with a treating haematologist on the basis of current blood test results. If invasive procedures are planned, such as extractions of teeth, dental plaque removal or endodontic treatment, local procedures should be supplemented with antibiotic prophylaxis. Teeth damaged due to decay process requiring sophisticated and long-term endodontic procedures, teeth following endodontic treatment if root canals are filled carelessly or periapical lesions are present, totally and partially retained teeth affected by pathological processes in surrounding tissues now or in the future, teeth affected by advanced paradentosis are qualified for extraction [15].

There are no standards for the prevention and treatment of OM [4]. All currently used measures are still investigated in clinical studies. Certainly, daily oral care is extremely important. For this purpose, tooth brushing 2–3 times a day or after every meal using ultra-soft toothbrush, ideally changed every day, are recommended in patients. Special dental pastes with a peroxidase system (e.g. Biotene) should be used. If the symptoms of xerostomia are present, this system helps to restore protective function of saliva and to prevent primary and secondary oral infections [8, 16, 17]. It is inadvisable to use toothpicks and dental floss due to additional soft tissue trauma [8]. Supplementary rinsing of the mouth 3 times a day is recommended using solutions with additives such as chlorhexidine and xylitol [17]. At the Haematooncology and Bone Marrow Transplantation Department of the Medical University of Lublin, it is used in a concentration of 0.2%, in a preparation Corsodyl, in combination with antifungal agent – amphotericin B (Fungizone) as a suspension. Chlorhexidine is thought to play a major role in regulating the amount of dental plaque, reduces the risk of tooth decay and gingivitis, and prevents fungal infections as well. It does not directly influence the treatment of OM [9]. One of the first symptoms of OM is very nagging pain. Local anaesthetics (diphenhydramine, lidocaine, dyclonine) as well as nonsteroidal anti-inflammatory drugs such as paracetamol are used in the management of it. In severe mucositis when the pain is very strong, opioids are given: morphine and derivatives and fentanyl, with the route of administration tailored individually to the needs of each patient (orally, intravenously, subcutaneously or sublingually) [8, 18]. The local use of the preparation called Caphosol is added to the above therapy. Caphosol mouth rinse contains calcium and phosphate ions, and helps to maintain proper hygiene of the oral cavity, keep it moist, and prevent oral mucositis (OM), if used regularly. Caphosol can be used in combination with other treatment options as it has no known interactions with other therapies. The studies have shown its high efficacy in the treatment of OM in patients receiving high-dose melphalan [19].

New methods of therapy

At the University Hospital of the School of Medicine of Ribeirao Preto, University of Sao Paulo (UHSMRP/USP), mouthwash was developed called ''Mucositis Formula''. It is used to treat the clinical symptoms of OM. ''Mucositis Formula'' is a combination of anti-inflammatory (benzidamine) and antifungal (nystatin) substances, anaesthetics (neututocain), and distilled water [5].

Pharmacological approaches to managing or alleviating the symptoms of OM are well supported by physiotherapy treatment, such as cryotherapy or laser treatment. The local application of cold results in the constriction of blood vessels, reduced flow of blood with high concentration of cytostatic agents, and thus, lowers their mucotoxic action.

It has been proved that the use of cryotherapy in patients treated with 5-fluorouracil decreases the risk of oral mucosa inflammation by 50%. Such results can be obtained when patients start to suck ice cubes 5 min before the administration of the drug, and continue to do so for the next 30 min of the therapy period. The benefits accruing from such approach are also observed in patients treated with high doses of drugs such as melphalan, metotrexate, edatrexate, etidronate, and in patients following the bone marrow transplant [8, 9, 18].

The studies have also confirmed the positive impact of helium–neon (He–Ne) laser in the prevention and treatment of OM in HSCT patients. Low-power laser therapy accelerates the epithelialization of lesions, decreases inflammation, is effective in fighting the pain, and stimulates salivary gland function [4, 17, 18].

A regards the prevention and treatment of mucositis, many hopes are pinned upon cytokines as they influence the course of inflammatory processes and immune response of the body [18, 20]. Pro-inflammatory cytokines, including IL-1, IL-2 as well as TNF, are thought to play a key role in the pathogenesis of OM. Currently, granulocyte-colony stimulating factor (G-CSF) and granulocyte–monocyte colony stimulating factor (GM-CSF) are used for therapeutic purposes. G-CSF is a glycoprotein that regulates the proliferation and differentiation of haematopoietic cells by increasing the number and stimulating the activity of neutrophils in peripheral blood, which shortens the duration of infection and neutropenia in persons undergoing myeloablative therapy before the autoHSCT [11]. There is no clinical evidence on the efficacy of the local use of the above preparations [20]. However, GM-CSF-synonym: CSF2, GMCSF, MGC administered by subcutaneous injection over 5–14 days during the chemotherapy, in particular if 5-FU, cisplatin, cyclophosphamide, doxorubicin and etoposide, methotrexate, vinblastine and

adriamycin are used, is effective in reducing the symptoms of mucosal inflammation [9]. The drug is discontinued after the white blood cell count is increased up to 1.0×10 [8].

Keratinocyte growth factor (KGF) is an important substance used systemically for the prevention and treatment of mucositis. Palifermin (Kepivance) is a human KGF produced in *E. coli* [18]. It influences the proliferation and reduces the apoptosis of epithelial cells, stimulates keratinocyte migration, and thus participates in the wound healing process. Palifermin at a dose of 60 μg/kg per day is recommended before the auto-HSCT. The drug should be started 3 days before the planned conditioning regimen, and continued for the subsequent 3 days following the transplant [20].

For the prevention and treatment of accompanying fungal infections, substances that reduce clinical symptoms of candidiasis in the oral cavity and gastrointestinal tract are used. These include nystatine, clotrimazole, amphotericin B, fluconazole [18].

It is thought that the prophylaxis for bacterial infections is extremely important in HSCT patients, as they are a common cause of complications and treatment failures. Suggested antibiotics include new-generation quinolones, levofloxacin and ciprofloxacin. These drugs show high activity and efficacy against Gram-positive bacteria and *P. aeruginosa*, and are of particular importance in the fight against infections in auto-HSCT patients [21]. Moreover, intravenous β-lactam antibiotics – third-generation cephalosporin (Biotum), aminoglycoside antibiotics – amikacin (Biodacyna), and fluoroquinolone chemotherapeitics – ciprofloxacin (Ciprofloksacin Kabi) are administered to treat infections at the Haemato-oncology and Bone Marrow Transplantation Clinic of the Medical University of Lublin.

Gastrointestinal symptoms accompanying high-dose therapy: nausea, vomiting, diarrhoea, require that the nutritional protocol be developed to be used in extreme cases of parenteral nutrition and in every case with antiemetic drugs (Torekan).

Preventive treatment

''In agreeing with the rule, that prevention is better than cure'', the comprehensive dental management should include the prophylaxis in a broad sense. It covers oral hygiene instructions, selecting appropriate dental pastes, brushes and mouthwash solutions, and frequent preventive exams. It is important to ensure long-term dental care on a regular basis to a patient after the transplantation, to make it possible to diagnose and prevent inflammation of the oral cavity that causes immune system disorders.

Summary

In general, mucositis should be treated conservatively to avoid further tissue irritation and damaging the remaining cells from which the epithelium will regenerate [9]. The effects of severe mucositis are so adverse, causing serious discomfort, lengthened hospital stays, additional hospital cost, and increased risk for infection and mortality. Further establishment of a methodology for oral health care in HSCT will be needed, and further research should focus on strategies directed at the prevention and treatment of OM [22].

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According to order.

Conflict of interest/Konflikt interesu

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Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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