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Acute radiation-induced oral mucositis in patients subjected to radiotherapy due to head and neck cancer

Abstract

Oral mucositis is a common side effect of radiation therapy for head and neck cancer. Severe mucositis is followed by symptoms, such as extreme pain, mucosal ulceration and consequent limitations in swallowing and achieving adequate nutritional intake. Mucositis may also increase the risk of local and systemic infection and significantly affect quality of life and cost of care. Severe oral mucositis can lead to the need to interrupt or discontinue cancer therapy and thus may have an impact on cure of the primary disease. In spite of all the advances made in understanding the pathophysiology of oral mucositis, there is still no prophylactic therapy with proven efficacy and known risk factors. This review will discuss oral mucositis epidemiology, impact and side effects, pathogenesis, scoring scales and prevention.

Keywords: acute radiation-induced oral mucositis, radiotherapy, head and neck cancer, toxicity.

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INTRODUCTION

Head and neck cancer (HNC) is one of the most prevalent malignant neoplasms in people. Annually, about 550.000 new cases of HNC are diagnosed and 380.000 deaths are attributed to this cancer worldwide [1]. In Europe, HNC accounts for about 4% of all cancers and annually there are approximately 250,000 new cases and 63,500 deaths [2]. In 2015 the incidence of HNC in Poland was 4.78 [3].

Despite the use of aggressive methods of treatment, only about 40-50% of patients with HNC survive for 5 years [4]. Hence, studies are being conducted aimed at intensifying the treatment of patients with HNC. Modification of chemical treatment regimens, introduction of new cytostatics or escalation of radiation dose as well as the use of unconventional dose fractioning and combining the above-mentioned methods lead to better treatment results, at the same time increasing the risk of developing acute radiation reaction in the mucous membranes of the head and neck area.

Acute radiation-induced oral mucositis develops in almost all patients irradiated for HNC [5]. The increased risk of acute radiation reaction occurs especially in patients treated with unconventional radiotherapy regimens (hyperfractionation or concomitant boost) or concurrent chemoradiotherapy, and the incidence of severe acute radiation reaction was observed in 75-90% of this population of patients [6,7]. Increased risk of acute radiation reaction was also observed in patients treated with cetuximab, the inclusion of which, in the standard radiation regimens in HNC patients, caused an increase in the frequency of clinically significant mucositis compared to conventional chemoradiotherapy [8].

The first symptoms of acute reaction usually appear within 10-14 days from the start of irradiation, after the administration of a dose of 10-20 Gy in conventional fractionation. The radiation-induced reaction within the mucous membranes develops gradually, thus not being a clinical problem in the first stages of its development. It manifests itself by intensifying symptoms of pain when swallowing and speaking, difficulties in taking food and liquids, oedema and ulceration. Significant disturbances and complications caused by the reaction occur at the time of its exacerbation when nutritional disorders, weight loss, impaired healing and necessity of parenteral nutrition are encountered [9]. The symptoms of severe radiation reaction often make patient hospitalisation necessary in order to implement intensive pain relief, supportive, anti-inflammatory and nutritional treatment. It was demonstrated that the cost of treatment of such a patient, depending on the severity of symptoms and related complications, ranges from $1.700 to $6.000 [10].

In 35% of irradiated patients, significant severity of radiation-induced symptoms makes it necessary to stop irradiation, which has the effect of limiting its effectiveness [11-14]. In a retrospective analysis of 2225 patients, it was demonstrated that an unplanned 1-day break in irradiation lowers the 2-year local disease control by 0.68% [14]. In turn, other authors have proved that each day of interruption in radiotherapy decreases local disease control by 1% [15,16].

This review will discuss acute radiation induced oral mucositis epidemiology, clinical manifestations, pathogenesis, scoring scales and prevention.

Risk factors for acute radiation induced oral mucositis

A number of factors that increase the risk of acute radiation reaction have been identified. There are two groups of such

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factors: a group of factors related to the ongoing therapy, such as the type of treatment (independent radiotherapy vs. chemo-radiotherapy), total radiation dose, irradiated area and volume, method of dose fractioning and a group of factors depending on the patient [17]. Factors depending on the patient have been evaluated, among others, in the study of Eilers et al. [18] (Table 1). It was shown that very young age, female gender, poor oral hygiene, reduced salivation, low BMI, renal function impairment with elevated serum creatinine and smoking increase the probability of acute radiation-induced oral mucositis.

Also, in the study of Chen et al. [19] including patients irradiated for oral cancer, it was confirmed that the increased risk of developing severe radiation reaction was characteristic in patients undergoing concomitant chemotherapy and radiotherapy ($p<0.05$), irradiated with a higher total dose ($p<0.01$), smokers ($p<0.01$), and patients with a low BMI ($p<0.05$). (Table 2).

Mechanism of acute radiation induced oral mucositis

The acute radiation reaction is caused by an imbalance between radiation-induced cell destruction and new cell production. To date, it has been estimated that 14 independent metabolic pathways are involved in the development of radiation reactions [11,12,20,21]. The most important of them include: nitrogen metabolism, activation of Toll-like receptor (TLR) signalling pathways, κB nuclear factor (NF-κB), B cell receptor, P13K/AKT signalling, cell cycle: G2/M DNA damage checkpoint receptor, p38 mitogen activated protein kinase (MAPK) pathway, activation of Wnt/B-catenin signalling pathway, signalling of the glutamate receptor, integrin, vascular endothelial factor, IL-6, death receptor (DR) and activation of SAPK/JNK signalling pathway [11,12,20,21].

In patients irradiated for head and neck cancer, the acute mucositis was described as a process developing in several phases [11,12,20,21]. In the first phase, the action of ionizing radiation leads to ionization (105 for each administered Grey per cell). In addition to direct damage of the DNA strand by electrons, the formation of free radicals (ROS-reactive oxygen species) also takes place. ROS action results in damage of cells, tissues and blood vessels and the development of inflammatory processes as well as the increase in the level of pro-inflammatory cytokines and chemokines. In the second phase of the reaction development, there occurs the activation of NK-kB nuclear factor and indirectly increased transcription of genes for pro-inflammatory cytokines: IL-6, IL-1B and TNF-α, which in turn induce and potentiate the inflammatory process, apoptosis and tissue damage caused by radiochemotherapy. In the third phase of the reaction, cell damage induced by the activation of the sphingomyelin-ceramide pathway through TNF-α intensifies and the synthesis of TNF-α, caused by the feedback that again activates NK-kB, increases at the same time. In the next phase, along with the accumulation of the radiation dose, there occur massive mucosal damage as well as mucosal and submucosal tissue losses, which lead to bacterial and fungal superinfection. The resulting activation of macrophages induces the release of proinflammatory cytokines and symptom severity increase [11,12, 20,21].

TABLE 1. Risk factors depending on the patient [18].

Age	Increased risk of severe radiation reaction at a very young age (high cell turnover) and old age (deterioration of repair processes)
Gender	Increased risk in women
Oral hygiene	Maintaining good oral hygiene reduces the risk
Salivary secretion	Reduced salivation increases the risk
BMI	Delayed healing processes in the case of malnourished patients
Renal function	Increased risk in case of abnormal renal function
Smoking	Delayed healing processes

TABLE 2. Risk factors depending on the patient and therapy [19].

Factors depending on the patient	Factors depending on therapy
Children and patients aged >50 years	Chemotherapy /dose, intensity, type of cytostatic/
Female gender	Radiotherapy /dose, dose fractioning method/
Malnutrition	Association of chemo- and radiotherapy
Xerostomia	
Pathological changes of the mucous membrane present before the start of radiotherapy	
Smoking, alcoholism	
Genetic predispositions	

Assessment of acute radiation induced oral mucositis

Currently, there are several scales used to assess the acute radiation induced oral mucositis. Three the most commonly used ones are: RTOG/EORTC, WHO and WCCNR.

RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) is a 5-grade scale that allows for the assessment of both early and late radiation reaction symptoms.

The World Health Organization (WHO) toxicity scale, in turn, measures anatomical, symptomatic and functional elements. It is easy to use, however, based on clinical observation of oedema, redness of the mucous membranes and assessment of the patient's ability to intake food via the oral route.

Another scale used is the one by the Western Consortium for Cancer Nursing Research taking into account only the anatomical changes associated with acute radiation reaction [22]. Table 3 presents a comparison of the most frequently used scales of acute radiation reaction.

TABLE 3. Comparison of the most frequently used scales for the evaluation of irradiation reaction.

Degree	0	1	2	3	4
WHO	None	Pain erythema	Erythema, ulcers, can east solids	Ulcers with extensive erythema, cannot swallow solids	Extensive inflammation of the mucous membrane, oral nutrition is not possible
RTOG	None	Erythema of the mucous membrane	A small reaction > 1.5cm, single	Converging, numerous lesions > 1.5cm	Necrosis or deep ulcers bleeding
WCCNR	Damages: none Colour: pink Bleeding: none	Lesions: 1-4 Colour: slight redness Bleeding: cannot be assessed	Lesions: >4 Colour: moderately red Bleeding: spontaneous	Lesions: numerous, continuous Colour: bright red Bleeding: spontaneous	Cannot be assessed

WHO, World Health Organization, RTOG, Radiation Therapy Oncology Group, WCCNR, Western Consortium for Cancer Nursing Research

One of the less frequently used scales is the Dische's scale. It is based on the observation of the radiation reaction occurring in the mucous membrane during hyperfractionated radiotherapy in patients with HNC. This three-grade scale sums up the assessment of symptoms, their intensity and the treatment used [26].

In turn, the OM Index (OMI) assesses the intensity of radiation reaction by evaluating symptoms such as erythema, ulceration, atrophy and oedema (for each element a scale from 0 to 3 has been determined, with the state of no symptoms classified as 0 and significant intensity of symptoms as 3). The OMI scale is characterized by a high degree of repeatability and reliability [27].

OM Assessment Scale (OMAS) is a highly reproducible grading scale for acute mucositis, sensitive and accurate in detecting symptoms associated with radiation reactions [28]. OMAS provides an objective assessment of the reaction depending on the presence and size of ulceration or the presence of croupous membranes (score 0-3: 0 = no lesion; 1 = lesion < 1 cm^2; 2 = lesion 1-3cm^2; 3 = lesion > 3cm^2), the assessment of erythema (score 0-2: 0 = none, 1 = moderate, 2 = severe) on the upper and lower lip, right and left cheek, right and left lower and lateral surface of the tongue, the bottom of the mouth, soft and hard palate [25,29].

Prevention of acute radiation induced oral mucositis

Oral mucositis induced by conventional cytotoxic therapies is a common and significant clinical problem in oncology.

Symptoms of mucositis, which include severe pain, may lead to dose reduction and unplanned interruptions in chemotherapy and/or radiotherapy, and often affect the quality of patient's life [30]. Maintaining good oral hygiene is the main preventive measure against the occurrence of acute radiation reaction, minimizing the risk of candidiasis or secondary bacterial infection, especially in hyperfractionated radiotherapy, complex CRT regimens or standalone RT [31].

Reduction in the risk of severe acute radiation reaction can be achieved by:

1. Maintaining good oral hygiene – it is one of the main factors determining the occurrence of radiation reaction and reducing its severity. It has been demonstrated that the formerly existing oral conditions, for example tooth caries, periodontal changes, pulpitis and xerostomia, affect the risk of increased bacterial colonization and increase the predisposition for the occurrence of severe radiation reaction. It is recommended to perform oral examination before starting treatment in patients with head and neck cancer. To minimize the oral side effects of anticancer therapy, it is recommended to eliminate all inflammatory and pathological oral conditions before the start of radiotherapy. This can be achieved by performing early histological, cytological and microbiological examinations [32].
2. The use of oral cryotherapy for 30 minutes, starting 5 minutes before the administration of 5-FU bolus. It has been demonstrated in clinical trials that it reduces mucositis associated with 5-FU chemotherapy [33,34]. It has been hypothesized that by reducing blood flow to mucosal tissues during administration of chemotherapy, the delivery of a cytostatic to the mucosa decreases, which results in less mucosal toxicity.
3. The use of the keratinocyte growth factor, which is an epithelial mitogen lowering ROS levels through the activation of the nuclear factor [35, 36]. It seems to be one of the promising options for treatment and prevention of mucosal complications that has been the subject of clinical trials [37].
4. Administration of amifostine which is an acceptor of free radicals, an antioxidant and a cytoprotective agent. It is usually administered intravenously before radiotherapy or chemotherapy. The substance was approved by the US-FDA in reduction of the incidence of moderate and severe xerostomia in HNC patients undergoing postoperative radiotherapy [38]. Injection of amifostine 60 minutes before radiotherapy in patients with HNC showed a marked decrease in adverse effects, unfortunately, with reduced treatment efficacy and patient response [39, 40]. In the case of moderate and severe xerostomia induced by radiation in patients with HNC, the recommended dose of amifostine is 200mg/m^2 once a day for 3 minutes before irradiation [41-43].
5. The use of low-energy helium-neon laser before irradiation showed a significant reduction in the duration and severity of acute radiation reaction in HNC patients [44].

CONCLUSIONS

Despite the great progress in the understanding of the pathomechanism of acute radiation reaction in patients irradiated for HNC, the implementation of prophylaxis and the use of modern and advanced methods of radiotherapy, the acute radiation reaction is still one of the greatest limitations of treatment in HNC patients. We still do not have a tool in everyday clinical practice to assess the risk of the development of severe radiation reaction in HNC patients undergoing radical radiotherapy. Therefore, multidirectional research is needed focused on the possibilities of limiting the radiation reaction that will determine effective prophylaxis and methods of treatment, but first and foremost concentrated on the determination of predictors of the occurrence of severe acute radiation reaction in patients treated for HNC. Due to the high individual variability observed in the occurrence and severity of acute radiation reaction indicating the essential role of genetic predisposition for this phenomenon, one of the current directions of research in this field is the evaluation of single nucleotide polymorphisms (SNPs) as a risk factor for the occurrence of the radiation reaction.

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