

CANCER THERAPY-INDUCED ORAL MUCOSITIS. A REVIEW OF EPIDEMIOLOGY, PATOPHYSIOLOGY, AND TREATMENT

Eugen Popa¹, Mihaela Pauna¹, Stefan-Ioan Stratul², Sergiu Ionita³

REZUMAT

Mucozita orală este o reacție adversă frecventă a terapiei radiante a cancerelor capului și gâtului, dar și a chemoterapiei. Mucozita poate restrânge toleranța pacientului la terapia antineoplazică, primejduind în același timp și statusul nutrițional. Astfel, tratamentul cancerului poate fi afectat în mod dramatic, la fel și calitatea vieții pacientului. Incidența mucozitei la pacienții sub tratament citostatic este de 40%, iar aceasta crește nu numai cu numărul sesiunilor de tratament, dar și cu numărul episoadelor anterioare de boală. În mod similar, 76% din pacienții cu transplant medular și cărora li se administrează doze mari de citostatice au șanse de a dezvolta mucozită. Pacienții supuși radioterapiei specifice carcinoamelor de cap și gât prezintă o incidență a mucozitei de 30-60%. Terapia antineoplazică interferează cu turnover-ul celulelor epiteliale, urmată de leziuni mucozale și infecții datorate invaziei indirecte de bacterii Gram-negative și specii fungice, întrucât cele mai multe medicamente anticanceroase sunt însoțite de modificări imunologice. Pentru a preveni și a trata mucozita orală, există mai multe opțiuni terapeutice, din păcate incomplet efective.

Cuvinte cheie: terapia cancerului, mucozită orală

ABSTRACT

Oral mucositis is a frequent adverse reaction of the radiation therapy of the head and neck cancers, as well as of chemotherapy. Mucositis may confine the patient's tolerance of antineoplastic therapy, and the nutritional status is endangered. Thus, the cancer treatment may be dramatically affected along with the patient's quality of life. The incidence of mucositis in patients treated with cytostatic drugs is 40% and this will not only increase with the number of treatment sessions but also with previous episodes of the disease. Similarly, a 76% chance of getting mucositis occurs in patients with bone marrow transplantation and who receive high doses of cytostatic medication. Patients which undergo radiotherapy, specific in head and neck carcinomas, display a 30-60% incidence of the oral mucositis. The antineoplastic therapy will interfere with the turnover of the epithelial cells, followed by mucosal injury, later by infections, due to indirect invasion of Gram-negative bacteria and fungal species, as most of the anti-cancer drugs cause immunological changes. In order to prevent and treat this condition many treatment options are available, but the complete, effective prevention and therapy cannot be achieved.

Key Words: cancer therapy, oral mucositis

INTRODUCTION

In the treatment of the head and neck cancers, chemo- and radiotherapy are the most widely used therapeutic procedures. They are associated with multiple side effects, although these treatments are designed to improve the patient's quality of life. Severe adverse effects following these therapies result in cancer patient morbidity and mortality. Besides, they

affect the economic activities of the patient. Annually, the incidence is of approximately 400,000 cases of treatment-induced oral lesions.¹ Oral complications subsequent to chemotherapy and/or radiation therapy include mucositis, xerostomia, infection (bacterial, fungal, or viral), particular neutropenia, dental caries, taste alterations, and osteoradionecrosis.²

Oral mucositis represents a major nonhematologic complication of cytoreductive chemotherapy and radiotherapy, associated with important morbidity, pain, odynodysphagia, dysgeusia, followed by dehydration and malnutrition.^{3,4} Severe oral mucosal affection can interfere with the normal of optimal cancer therapy protocols. For example, dose reductions or treatment schedule modifications may be necessary in order to allow the resolution of oral lesions. The treatment is then usually discontinued in cases of severe oral morbidity, when the patient is no longer able to resume the antineoplastic therapy. These interruptions in dosing regimens secondary to oral complications can negatively affect the overall patient prognosis.

¹ Department of Removable Prosthodontics, Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, ² Department of Periodontology, Faculty of Dental Medicine, Victor Babes University of Medicine and Pharmacy, Timisoara ³ Department of Fixed Prosthodontics, Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest

Correspondence to:
Eugen Popa, Faculty of Dental Medicine, 19 Calea Plevnei, Bucuresti, Tel. +40-21-3158649.
Email: epopa70@clicknet.ro

Received for publication: Feb. 22, 2008. Revised: May 19, 2008.

EPIDEMIOLOGY

Incidence as well as severity may vary individually. The chance of developing mucositis is dependent upon the therapeutic agent. Berger and Kilroy estimated that about 40% of patients which undergo chemotherapy develop mucositis.⁵ This risk grows with the number of therapy cycles and previous episodes of mucositis. Drugs interfering DNA synthesis (S-phase-specific agents such as fluorouracil, methotrexate, and cytarabine) develop more significant cytotoxic effects.⁶ Studies by Peterson and Wilkes estimated that with bolus and continuous infusions there is an increased risk of mucositis, compared to prolonged or repetitive regimens of lower doses of cytoreductive agents.^{6,7} In patients with bone marrow transplantation the risk of oral mucositis is around 76%. Thirty to sixty percent of patients which undergo radiation therapy for head and neck cancer may be affected by mucositis, and more than 90% of patients receiving chemoradiation therapy, as well.⁸ The severity and duration of mucositis in patients treated with radiotherapy are connected to the type of radiation source, the total dose, the dose intensity, the amount of the irradiated mucosa, smoking, alcohol ingestion, and level of oral hygiene.^{9,10} In patients treated with standard 2 Gy of daily fractionated radiotherapy programs, mucosal erythema occurs in the first seven days. Mucositis (patchy or confluent) peaks after 4-5 weeks of treatment with the same dose of radiation. In case of daily fractionated programs with less than 2 Gy, the severity of mucositis might be low. In spite of this, in accelerated radiotherapy programs, mucositis increase in gravity at 21 days. Interstitial radioactive implants cause mucositis usually in 7-10 days and peaks after 14 days.¹¹

PATHOPHYSIOLOGY

The exact pathophysiologic development of mucositis is not exactly elucidated, but it is thought that it is based on two mechanisms: direct mucositis and indirect mucositis. Direct mucositis is related with chemotherapy and radiation therapy interference with the maturity and cellular growth of epithelial cells, who present a rapid turnover, every 7-14 days. Thus, these cells are susceptible to the effects of cytotoxic therapy and finally appear changes to normal turnover and cell death.⁵ Indirect invasion of Gram-negative bacteria and fungal species can cause the indirect mucositis. The neutropenic patients have an increased risk of oral infection. The onset of indirect

mucositis varies, and is related with the timing of the polymorphonuclear granular leukocytes nadir, associated with the cytoreductive agent administered, but usually develops anywhere from 10-21 days after the onset of the chemotherapy regimen.¹²

Based on the above consideration, new pathophysiologic mechanisms have been established. The mechanism of mucositis involves four phases:¹³

Phase I is the initial inflammatory/vascular phase. During this phase, in the buccal mucosa are released free radicals, modified proteins, and proinflammatory cytokines, including interleukin-1B, prostaglandins, and tumor necrosis factor (TNF) by the exposed cells (epithelial, endothelial, and connective tissue cells). The inflammatory mediators cause further damage, directly or indirectly, by increasing vascular permeability, thereby enhancing cytotoxic drug uptake into the oral mucosa.¹⁴

Phase II is the epithelial phase. In this phase, antineoplastic therapy inhibits cell division in the oral mucosal epithelium, followed by a reduced epithelial turnover and renewal, resulting in epithelial breakdown. The erythema appears from increased vascularity and epithelial atrophy 4-5 days after the beginning of chemotherapy. At this stage, the microtrauma caused by regular daily activities such as mastication, swallowing, and speech leads to ulceration of the oral mucosa.

Phase III is the ulcerative/bacteriological phase (pseudomembraneous). Breakdown of the oral epithelium ultimately results in an ulcerative stage, which occurs within 7 days of therapy. Epithelial loss and furious exudation lead to the formation of pseudomembranes and ulcers. (Fig. 1) Thus, microbial colonization of the damaged mucosal surfaces by Gram-negative organisms and yeast occurs, and this may be exacerbated by concomitant neutropenia.



Figure 1. Typical form of oral mucositis.²⁷

Infectious complications arising in neutropenic bone marrow transplantation recipients are among

the most challenging aspects of aggressive myelo-suppressive antineoplastic drug therapy. The ulcerative mucositis is an important etiologic factor in the development of systemic streptococcal infections in the neutropenic cancer patients.¹⁵

Phase IV is the healing phase. Its duration is usually 12-16 days, and depends mainly on factors such as epithelial proliferation rate, hematopoietic recovery, reestablishment of the local microbial flora, and absence of factors interfering with the wound healing.¹³

TREATMENT OPTIONS AVAILABLE FOR ORAL MUCOSITIS

Prophylactic measures

Patients who maintain a correct oral hygiene suffer less severe degrees of mucositis, and its duration is frequently shorter than in patients with bad oral habits.^{16,17} The prevention, identification and early treatment of oral lesions is of paramount importance for ensuring adequate patient quality of life, although mucositis improves after resolving the neutropenia. The nursing personnel must instruct the patient on careful oral hygiene. Thus, the influence of local irritants (physical, chemical or thermal) can be avoided. The following prophylactic and diagnostic steps are indicated:

a. Avoidance of wearing removable dentures, which serve as reservoirs for microorganisms, especially *Candida* species, in the acute phase of mucositis. Also apply here measures of oral hygiene involving chlorine-releasing products or chlorhexidine digluconate.

b. Assessment of the benefits of the orthodontic treatment (both fixed and removable) and the inherent irritating actions they may exert upon the oral cavity of the patient. The patient orthodontist should be consulted.

c. Mouthrinses without alcohol. Chlorhexidine digluconate (a broad spectrum antibacterial agent which is also active against *Candida* species) can be applied in solution form at concentrations of 0.12% and 0.2%. The lesser concentration is supplied as a mouthrinse, while the 0.2% presentation is used as a bioadhesive gel.¹⁸⁻²⁰ Carbonated water ensures an alkaline salivary pH, which contributes to counteract the growth of *Candida* species and acid etched enamel decalcification. Hydrogen peroxide diluted in equal proportions of water helps clear food remains and detritus that accumulate on the teeth and mucosa.

d. Soft foods at room temperature are indicated for avoiding thermal or frictional trauma. Low-carbohydrate

diets are advisable to prevent the formation of caries.

e. High fluid intake contributes to improve salivation.

f. Careful dental and gingival hygiene is indicated, provided the platelet count is over 5×10^9 platelets/l, using a very soft tooth brush. Toothpaste should be avoided above mucositis grade I. Fluorated toothpastes and brushing with a soft brush is acceptable in periods without mucositis.²¹

Therapeutic attitude

In 1979, the World Health Organization (WHO) defined the degree of mucositis according to the severity of the lesions.²² Five grades were established (from 0 to IV), grade 0 representing the absence of lesions and grade IV the presence of severe lesions in terms of extent and depth: 0 = normality; I = generalized erythema (painless pink mucosa with abundant saliva and normal voice function); II = erythema involving small ulcerations and preserved solid swallowing capacity; III = extensive ulcers with edematous gingival tissue and thick saliva, preserved liquid swallowing capacity, pain and speech difficulties; IV = very extensive ulcers with bleeding gums, infections, the absence of saliva, incapacity to swallow, and intense pain.

The treatment indications are based on the grade of mucositis, and therapy corresponding to one grade higher than that established at initial diagnosis is to be provided:

- Grades 0 and I: The patients should be instructed on the following hygiene measures: (a) correct and gentle tooth brushing after meals; (b) chlorhexidine digluconate mouth rinsing after brushing; (c) fluid intake to maintain salivation; and (d) preservation of lip integrity by applying topical vaseline;

- Grade II: The treatment measures defined for mucositis grade 0 and I are to be applied every 4 hours, adding carbonated water and nystatin solution (5 ml every 6 hours) as rinses.²³⁻²⁵ The patient is wearing removable dentures only during mealtimes;

- Grades III and IV: The treatment measures defined for mucositis grade II are to be complemented with the topical and systemic treatments indicated according to the etiology of the lesions. Fungal infections of the oral cavity are to be treated with nystatin solution (5 ml every four hours) and fluconazole in solution (200 mg/day via the oral route).¹⁸⁻²⁰ In turn, local herpetic infections should be treated with aciclovir cream (5 applications a day). Lastly, ulcerations are to be treated locally with 4-6 daily applications of any of the following magistral formulations: (a) 0.1% fluocinolone

acetone in orabase; (b) 0.1% triamcinolone acetone in orabase; or (c) 1% hydrocortisone in orabase.

Patient education is very important in managing chemotherapy-induced and/or radiation-induced mucositis. Patients should be motivated to follow guidelines indicated below, to reduce the discomfort caused by mucositis:

- Feel encouraged to sit upright at a 90° angle and lean the head slightly forward.

- Eat slowly. Food must be cut in to small pieces and chewed completely.

- Eat small frequent meals instead of heavy meals.

- Food taken should be warm, or at room temperature. Hot food and drinks should be avoided. Similarly, crunchy foods such as potato chips and nuts should also be avoided.

- Soft food is always encouraged. Finely chopped cooked meat, fruits, and vegetables should be taken. Patients can also try commercial baby foods, which are nutritious, convenient, and very easy to swallow. Milk shakes that have very high proteins can also be tried.

- Usage of straw will not only make drinking easy but will also avoid direct contact with the affected portion.

- Do not talk while food is in the mouth.

- Acid foods such as tomatoes, grapes, apple fruits or juices, alcohol and tobacco, and spicy foods should be avoided.

- In order to relieve discomfort of dry mouth, patients are asked to rinse mouth with water before and after every meal.²⁶

CONCLUSIONS

Oral mucositis is a serious and challenging complication of cytoreductive therapy in cancer patients. Because the treatment of mucositis is limited, prophylaxis is stressed. Patient education with regard to oral hygiene is emphasized. It's important also the assessment of the patient's psychological condition, in particular depressive disorders. This is important because treatments with antidepressive medication will not only contribute to lift the depression, but also to reduce the pain somatization. Although mucositis is rarely life-threatening, it will interfere, to a great extent, with the outcome of the cancer treatment.

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