

Current strategies for the management of oral mucositis induced by radiotherapy or chemotherapy

Estratégias atuais para o controle da mucosite bucal induzida por radioterapia ou quimioterapia

Abstract

Oral mucositis is a clinically relevant complication during the treatment of cancer patients. It is frequently seen in subjects receiving high doses of radiation therapy in the head-neck region, chemotherapy or a combination of these treatment modalities. Due to its complex pathophysiology, this type of inflammation can also affect the gastrointestinal tract, which has attracted the attention of medical professionals. The oncologic treatment does not distinguish the malignant cells from the normal epithelial cells of the mucosa because of their high-proliferative capacity. Thus, the mucosa becomes atrophic and more susceptible to trauma, allowing the development of inflammation and installation of secondary infections, which aggravates the patient clinical conditions and reduces the quality of life. The clinical management of mucositis includes preventive and palliative strategies. The preventive measures are the education and monitoring of patients in relation to their oral hygiene. The palliative measures should be adopted as early as the mucosa lesions occur and involve the use of oral solutions, topical anesthetics, analgesics and anti-inflammatory agents, lasertherapy, cryotherapy, and other clinical alternatives to control mucositis and provide comfort to the patient.

Key words: Mucositis; chemotherapy; radiotherapy; cancer

Resumo

A mucosite bucal é uma importante complicação do tratamento de pacientes oncológicos e, frequentemente, acomete uma parcela dos pacientes submetidos a altas doses de radiação na região de cabeça e pescoço e/ou quimioterapia ou à combinação de ambas. Em função de sua complexa fisiopatologia, esse tipo de inflamação também pode afetar a mucosa gastrointestinal e vem recebendo grande atenção por parte de cirurgiões-dentistas e médicos. Sabe-se que o tratamento oncológico, além de agir sobre as células malignas, também tem ação sobre as células epiteliais da mucosa, em razão de sua alta capacidade proliferativa. Dessa forma, a mucosa torna-se atrófica e suscetível a traumas, possibilitando o desenvolvimento da inflamação e a instalação de infecções secundárias, agravando o quadro clínico do paciente e reduzindo sua qualidade de vida. Há uma preocupação no controle da mucosite por meio de medidas preventivas para impedir seu desenvolvimento e de medidas paliativas, quando esta estiver instalada. Dentre as medidas preventivas estão a educação e o monitoramento do paciente visando o cuidado com a higiene bucal, enquanto as medidas paliativas envolvem o uso de soluções enxaguatórias, anestésicos tópicos, antiinflamatórios e analgésicos, laserterapia, crioterapia e outras alternativas. Essas medidas constituem estratégias que visam controlar a mucosite e propiciar melhor qualidade de vida ao paciente.

Palavras-chave: Mucosite; quimioterapia; radioterapia; câncer

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Introduction

Oral mucositis is considered an acute inflammation caused by the necrosis of the basal layer of the oral mucosa (1). It is one of the most common oral complications associated with cancer treatment (chemotherapy and/or radiotherapy). The more important clinical features are erythema and/or ulceration (2), which may extend from the mouth to the rectum (3). It can induce several life-threatening complications, such as intestinal obstruction and perforation (4), reducing the patient's quality of life and leading to severe infections, which may require the interruption of the antineoplastic treatment (5). Oral and throat pain caused by the mucosa ulceration, abdominal pain, vomits and diarrhea are characteristics that compromise the patient's nutritional status because of a decrease of food intake, leading to weight loss (6). The progression of oral lesions and its impact on general conditions of the patient may require parenteral nutrition or temporary interruption of the antineoplastic treatment (7).

The incidence and severity of mucositis depend on the patient features and the kind of cancer treatment (5). Traditionally, oral mucositis has been more related to hematologic malignancies than to solid tumors, because the incidence of severe mucositis is higher for the first (6). It results from the direct cytotoxicity of the chemotherapy drugs on the mucosa cells or on the hematopoietic system (5). As oral mucositis is considered an important side effect of cancer treatment, the search for new and more effective alternatives for its control has been the aim of several studies (8).

Epidemiology and pathophysiology

Mucositis has received significant attention from the physician community in the last two decades. However, standardized protocols for its prevention and control have not been developed yet. It is estimated that oral mucositis affects 40% of the patients undergoing chemotherapy, 75% of the patients undergoing high dose chemotherapy and bone marrow transplantation and more than 90% of the patients undergoing radiotherapy for head and neck cancer (9). Oral and gastrointestinal mucositis can affect 100% of the patients undergoing high doses of antineoplastic chemotherapy or bone marrow transplantation, 80% of the patients with malignant tumors in the head or neck region and undergoing radiotherapy treatment, and also 50% of the patients undergoing chemotherapy (4). According to Chiappelli (1), 40% of the patients undergoing chemotherapy or radiotherapy will develop mucositis. It is a condition that directly affects the patient's quality of life because of its multiple clinical signs and symptoms (3,10) (Fig. 1).

Some studies suggested that the pathophysiology of oral mucositis is very complex and includes direct effects of anticancer agents on the epithelium cells, in addition to the action of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). Many other factors interfere in this process, such as

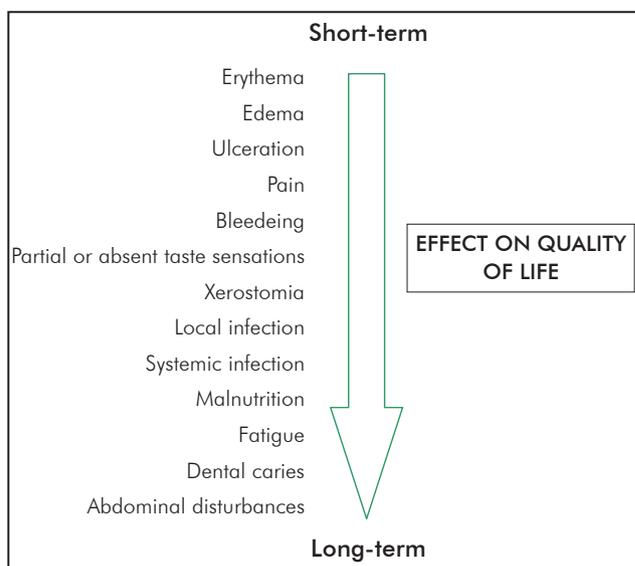


Fig. 1. Effects of symptoms of oral mucositis on short- and long-term quality of life (Source: Stone et al., 2005).

the oral microorganisms, the immune status of the patient, the overlap of local trauma, and the oral hygiene conditions. Moreover, it was suggested the possibility of a genetic polymorphism in inflammatory responses, which would make one person more susceptible to mucositis than the others (11).

Firstly, the chemotherapy drugs induce the death of the basal epithelial cells, which may occur by the generation of free radicals. These free radicals activate second messengers that transmit signals from receptors on the cellular surface to the inner cell environment, leading to up-regulation of pro-inflammatory cytokines, tissue injury, and cell death. The pro-inflammatory cytokines produced by macrophages, such as TNF- α , amplify the mucosal injury; the production of these pro-inflammatory cytokines can also be stimulated by a superimposed infection of the ulcerated areas of the mucosa. Later, epithelial proliferation and cellular differentiation occur, restoring the integrity of the mucosa (12).

The first symptoms reported by patients with oral mucositis are burning mouth and color changes in the mucosa, which becomes white because of insufficient keratin desquamation. Then, this epithelium is replaced by atrophic, edematous, erythematous, and friable mucosa, allowing the development of ulcerated areas with the formation of a pseudomembrane, characterized by the presence of a fibrinopurulent, yellow, and outstanding layer (2,5). The ulcerated lesions are painful and compromise the patient nutrition and oral hygiene, and also are considered sites for the development of local and systemic infections (12).

In some cases, abnormal bleeding can occur due to thrombocytopenia and neutropenia caused by bone marrow suppression. Furthermore, intestinal or liver damage may decrease the levels of vitamin K and coagulation factors, with consequent increase in the time of bleeding. The tissue damage can induce the production of thromboplastin at high

levels causing disseminated intravascular coagulation; so petechias and ecchymosis are common. The sites most frequently involved are those submitted to the daily trauma during mastication and other oral functions, the regions with non-keratinized mucosa, such as tongue, vermilion border, soft palate, and mouth floor, but other sites of the oral mucosa can be affected (13).

The ulcerations may allow the entry of bacteria and other pathogens, which could lead to secondary infections, such as local infection by *Candida albicans*. Patients with chemotherapy-induced neutropenia and mucositis also are at high risk for bacteremia and sepsis (1). Infections are the major cause of mortality among cancer patients who are immunosuppressed due to the side effects of cancer therapy. The lower resistance of the host generates changes in the oral microbiota, allowing the proliferation of some opportunistic pathogenic microorganisms, providing quantitative and qualitative changes and consequent imbalance in the ecosystem. Viral infections, such as herpes simplex and those caused by fungi, can be superimposed on mucositis but they are not considered as etiological agents, although they can complicate the diagnosis of mucositis and its control (12). The hospitalization during the chemotherapy cycles is significantly longer in patients with gastrointestinal and oral mucositis; this factor is also related to a greater number of deaths from infection (12). Patients with oral mucositis may have severe pain and loss of 5% or more of body weight (14). Furthermore, after the tissue repair process, even though the mucosa presents normal appearance, its structure will be more fragile physiologically. In the small intestine, for example, there is a significant loss of absorptive capacity (6).

The mucosal response to cancer therapy cannot be predicted clinically because the onset of oral mucositis is influenced by several factors. A certain dose of cytotoxic drugs or radiation can produce severe oral reactions in some patients, while no change is found in others. Many risk factors are involved in the development of mucositis and can be divided into two categories (3,8): those related to the patient condition and those related to cancer therapy (15).

Some patient-related risk factors are: age (children are more susceptible to oral mucositis because of their high epithelium turnover, and the elderly are susceptible because of their low capacity of mucosa repair), sex, nutritional status, xerostomia, previous mucosa lesions, periodontal disease, tobacco use and alcohol intake, oral hygiene status, neutropenia (15), use of inducing drugs, genetic predisposition, and previous episodes of oral mucositis.

Among the factors related to the cancer therapy are: type and combination of treatment modalities, number of recommended doses, intensity, duration and frequency of therapy (5,8). The chemotherapy by continuous and frequent infusions, during intermittent periods, is more likely to induce mucositis than the use of a single and low dose of the chemotherapy drug (1). According to Sonis (11), mucositis is more likely to occur in younger patients, such as children under 12 year-old, because of the higher mucosal

turnover. The identification of patients at risk to develop mucositis allows the early implementation of preventive measures (15).

The radiotherapy and chemotherapy in patients with oral mucositis require special care, such as total parenteral nutrition, replacement of fluids, pain control, and prophylaxis against infections (3,14). The severity depends on the dose of chemotherapy, fraction of doses, volume of treated tissue, type of radiation, previous or concurrent chemotherapy-radiotherapy, and presence of systemic diseases, such as diabetes mellitus or vascular disorders (5).

According to the World Health Organization, oral mucositis is classified into the following grades: grade 0 – absence of mucositis; grade I – presence of painful ulcerations and erythema; grade II – presence of painful, erythema, edema or ulcerations that do not affect the patient food intake; grade III – confluent ulcerations that affect the food intake; grade IV – the patient requires parenteral nutrition (11).

Current strategies for the management of oral mucositis

Many different treatment protocols are available to prevent and/or reduce the severity of oral mucositis, although there is little evidence to recommend one or another approach as a gold standard procedure (16). The control of oral mucositis can be divided into two groups of procedures: the first covers the control of pain, nutritional support, oral care, palliative treatment for xerostomia, and control of oral bleeding, and the second group refers to therapeutic interventions (12).

In general, management of oral mucositis has been essentially palliative (17). Despite the relatively high prevalence and severity of mucositis, the usual measures for its management are restricted to relief of painful symptoms and maintenance of good oral hygiene (3). Mucositis requires an expensive treatment when it reaches the advanced stage of development. Mucositis grades III or IV lead to a greater number of hospitalizations, major complications, high costs and mortality rates; these consequences cannot be reduced by palliative strategies and analgesics (6). In some cases, the management of mucositis requires the interruption of the anticancer therapy for up one week (1).

Strict oral care to reduce potential pathogenic microorganisms is mandatory for mucositis prevention and management. Dental caries, periodontal disease, and other infections should be treated before any anticancer therapy (18). It is essential to educate the patient to adopt a standardized protocol of oral hygiene (8,10,19) before the chemotherapy and/or radiotherapy (18). The maintenance of good oral hygiene reduces pain, bleeding, infections, and risk for possible dental complications (4). Therefore, the patient and family, doctors, and nurses should be aware of the importance of having a good oral hygiene during the cancer treatment; frequent assessment of the oral cavity is recommended, especially for those patients at high risk to develop mucositis (6).

Tooth brushing is necessary at least twice a day with a new brush for each chemotherapy cycle. The patient should be advised to use dental floss daily and rinse the mouth with clean water. Use of oral solutions, such as saline solution, sodium bicarbonate or a mixture of both, can also be recommended (20). Moreover, consumption of spice foods, tobacco and alcohol, use of oral mouthrinses containing alcohol should be avoided (6,10,18), and adequate hydration should be maintained (6,19).

When mucositis is present, soft and liquid diet should be established, because it is more easily tolerated than a normal diet (12). Refined carbohydrates are a good source of energy, but changes in taste resulting from the cancer treatment limit the intake of sugars. It is recommended to increase the intake of protein, such as meat, fish, and eggs; foods that exacerbate diarrhea should be avoided (6). The use of topical antibiotics may be effective to prevent radiotherapy-induced mucositis (11).

According to Wong et al. (21), patients with head and neck cancer undergoing radiotherapy may use some self-care measures to relieve painful symptoms: use of analgesics, mouthwashes to lubricate the oral cavity, mouthrinse solutions, drug applications on the ulcerations, discontinued use of prostheses, changes in diet, and others. The medication most often used by patients undergoing radiotherapy was the combination of acetaminophen with codeine (58%). Also, systemic opioid analgesics are used, but the patient should be hospitalized, which can increase complications and treatment costs (16). Intravenous morphine is the recommended first-line therapy to relieve severe pain. This can be administered using a system of patient-controlled analgesia, with lower doses and a shorter duration of opioid therapy, under careful monitoring by skilled nurses (4,6,10,19). The use of adjuvants can replace or improve the action of opioid analgesics for pain management: cyclooxygenase-2 inhibitors and other NSAIDs, gabapentine, cannabinoid, receptor alpha-2-adrenergic agonists, such as clonidine, nicotine, lidocaine, and ketamine (20). Keefe et al. (6) and Rubenstein et al. (4) recommended the use of omeprazole and ranitidine to prevent epigastric pain after chemotherapy with cyclophosphamide, methotrexate, and 5-FU.

Topical anesthetics include 2% viscous lidocaine in combination with other agents, such as difenhydramine, kaolin, milk of magnesia, or chlorhexidine, and used in mouthwashes (4,16). It has been suggested that topical anesthetics would act on the taste buds removing the flavor perception, and they can also change the swallowing reflex because its action on the oropharyngeal mucosa (20).

Chlorhexidine would reduce the microorganism populations because of its antibacterial and antifungal activity, but its use is not indicated because of side effects, such as inflammation, oral discomfort, dysgeusia, and dental pigmentation (12). The use of chlorhexidine is not recommended for prevention of mucositis in patients with solid head and neck tumors undergoing chemotherapy and radiotherapy (19).

Topical application of benzidamine, a non-steroidal anti-inflammatory drug with cytoprotective, antimicrobial, and analgesic action, relieves the pain and reduces the use of opioid analgesics (4,20); it inhibits pro-inflammatory cytokines, including TNF- α (12); it is considered a safe product, although its effectiveness for prevention of mucositis induced by chemotherapy agents is still unknown (19). However, the use of other agents, such as doxepin, morphine, and topical capsaicin, also has a beneficial effect through the inhibition of substance P involved in the activation of nociceptors during the inflammatory process (16).

Patients with xerostomia – which results from the chemotherapy action on the salivary glands and causes hiposalivation or total disability in the saliva production – often use palliative measures, such as: use of artificial saliva or frequent ingestion of water to relieve the discomfort, mouthwashes with sodium bicarbonate to clean and lubricate the oral cavity, use of sugarless chewing gum to stimulate salivation, and use of cholinergic agents, if necessary (12). Use of anticholinergic or sympathomimetic agents that would further reduce salivary flow rates should be avoided (18). Bleeding associated with ulcerated lesions can be controlled with the use of topical hemostatic agents, such as fibrin glue. Patients with platelet count less than 20.000/mm³ cannot receive blood transfusion because of the risk of internal bleeding (12).

In a pre-clinical study by Goulart et al. (22), the amniotic membrane was shown to be a biocompatible product with the capacity to adhere to ulcerated mucosa surfaces, accelerating the healing process by its antiinflammatory activity. In the same study, it also was found that the amniotic membrane promotes rapid cell proliferation, especially of fibroblasts and epithelium cells, and stimulates vascular neof ormation that positively influences the repair process. This proliferative capacity is probably due to the presence of stem cells and growth factors.

Octreotide is an analogue of somatostatin that regulates intestinal electrolyte balance, inhibits some hormones (serotonin, intestinal vasoactive peptide, insulin, secretin, glucagon, and pancreatic polypeptide) and preserves the epithelial barrier function. So subcutaneous administration, twice a day, of 100 mg of octreotide reduces diarrhea induced by chemotherapy (4). Peterson et al. (19) recommended the use of omeprazole to prevent epigastric pain. Other topical agents, such as sucralfate and dibucaine, have been studied. Rubenstein et al. (4) and Peterson et al. (19) did not approve the use of these agents because of their possible side effects.

Rashad et al. (23) reported that the prophylactic use of pure natural honey was effective to reduce oral mucositis in patients with head and neck cancer undergoing radiotherapy. The authors showed that honey can reduce the incidence of grades III and IV radio-chemotherapy-induced mucositis, because it accelerates the epithelium repair when applied topically; it is an economical and accessible substance with bacteriostatic properties.

In recent studies, the growth factors such as tetra-chlorodecaoxide, granulocyte-colony stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and transforming growth factor- β 3 (TGF- β 3) demonstrated benefits on pain relief and mucosa repair, reducing mucositis by their action on polymorphonuclear neutrophils (16). However, they are very expensive (8). In addition, it was described in the literature the use of palifermin, a recombinant human keratinocyte growth factor that mediates the epithelial cell growth and repair, reducing cell apoptosis and the production of TNF- α (16). Its use has been approved in the United States to reduce the incidence and duration of severe mucositis in patients with hematologic malignancy, which were submitted to high-dose chemotherapy regimens or bone marrow transplantation (10). A dose of 40 mg/kg/day for three days has been recommended for the prevention of oral mucositis in patients receiving 5-FU associated with leucovorin; and a dose of 60 mg/kg/day for three days has been prescribed to patients under high dose chemotherapy or subjected to bone marrow transplantation (19). Some adverse effects are ulcerations, itching, erythema, paresthesia, oral disorders, and tongue with swelling and dysgeusia (8). According to Oelmann et al. (24) a concern about the use of growth factors in the treatment of mucositis is the ability to stimulate the proliferation of tumor cells, although the expression of cellular receptors has been identified in well-differentiated cells.

Low-energy laser radiation used prophylactically during radiotherapy can reduce the incidence and severity of mucositis, pain, and functional damage in patients under high dose chemotherapy or in radio-chemotherapy previous to bone marrow transplantation (7,19). This kind of treatment promotes healing and reduces pain, does not show any toxicity or trauma to the patient, but requires expensive equipment (8).

Cryotherapy has been recommended especially for patients under administration of 5-fluorouracil (4). It reduces blood flow and allows a little amount of the chemotherapy agent in the oral mucosa by promoting temporary vasoconstriction. The ice chips are used by patients for 30 minutes, 5 minutes before chemotherapy with 5-FU and melphalan (4,6,19). The advantages of this alternative are the simplicity, low cost, and absence of toxicity (4,8).

Glutamine is an aminoacid necessary for cell mitosis and it only acts in the prevention of mucositis by reducing the production of pro-inflammatory cytokines related to cell apoptosis. The use of Gelclair® (OSI Pharmaceuticals, Melville, New York, USA), hyaluronic acid gel, promotes pain relief, because it forms a protective layer that covers the

ulcerations, providing less discomfort during the ingestion of food (19).

The administration of parenteral amifostine reduces the levels of pro-inflammatory cytokines, reducing the degree and severity of mucositis, but it does not prevent the suspension of parenteral nutrition and the use of analgesics (11). However, it was recommended to minimize esophagitis induced by concurrent chemotherapy and radiotherapy and the incidence of xerostomia associated with mucositis (19). Nevertheless, its toxicity is a great disadvantage, because it can generate nausea, vomits, hypotension, sneezing, sleepiness, dysgeusia, allergic reactions, and hypocalcemia. Currently, amifostine is approved only for the reduction of renal toxicity associated with repeated doses of cisplatin in patients with advanced ovarian cancer or with lung cancer and to reduce the incidence of xerostomia in patients undergoing radiotherapy for head and neck cancer (4).

The use of medicinal herbs and natural products has also been reported, as the mixture of the pentacyclic triterpenes alpha and beta-amyrin isolated from the resin of *Protium kleinii* plant, which act as anti-inflammatory and anti-nociceptores (25).

Final Considerations

Mucositis is a common side effect of radio and/or chemotherapy anticancer treatments, but it has a complex pathophysiology and requires management strategies that have not been standardized yet. To identify patients at high risk to develop this condition is essential to reduce the costs of the anticancer treatment and to avoid its interruption after the installation of mucositis. There are many agents used for the treatment of mucositis with different mechanisms of action. However, there are no conclusive evidences on their effectiveness to establish protocols for patients undergoing radio and/or chemotherapy.

Additional clinical studies are necessary to determine the effectiveness of these agents for the prevention and treatment of oral mucositis. Despite the large number of published studies, there is still no gold standard to be used routinely for the management of acute pain from mucositis. It is essential to evaluate agents with different mechanisms of action that can be used together to improve the clinical results, providing better quality of life for the cancer patients. Therefore, the treatment of mucositis does not depend on the use of a single drug, but on the rational use of different treatment modalities. The combination of drugs in sequential levels, according to the administration of chemotherapeutic agents and radiotherapy, may be an effective approach for the management of oral mucositis.

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