



Prevention and management of oral complications of head and neck cancer treatment

Prevenção e manejo das complicações bucais do tratamento oncológico de cabeça e pescoço

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Abstract

Introduction: Radiotherapy (RT) and chemotherapy (CT) are therapeutic methods widely used in patients with malignancies in the head and neck regions. However, these therapies are able to induce significant acute and late toxicities to oral structures and their surrounding tissues. **Objective:** To describe the acute and chronic oral complications of RT and CT in head and neck, showing the way the dental professional can manage them. **Materials and methods:** Virtual Health Library (VHL) – Bireme: LILACS, IBECS, MEDLINE and BBO, PubMed, SciELO, Brazilian Digital Library of Theses and Dissertations (BDTD), Capes database journals and renowned oral medicine books were searched. The search strategies used included the following keywords: radiotherapy, chemotherapy, adverse effects and treatment. Thirty-two references were selected between 1990 and 2012 for the development of this review. **Results:** Both therapies are associated with adverse effects that significantly affect the patients' quality of life. Their adverse effects are dose-dependent and may occur since the first week of treatment. The most important complications are included the oral mucositis, radiodermatitis, hyposialia, hypoguesia, radiation caries, opportunistic infections, developmental abnormalities, osteoradionecrosis and trismus. A preliminary evaluation of the oral health status and the accompanying by the dentist during treatment may act to prevent and reduce the damage to oral tissues. **Conclusion:** The multidisciplinary treatment, including medical team, dental surgeon, speech therapist,

psychologist and nutritionist is the best alternative to minimize or even prevent many complications resulting from physical and psychological anticancer treatment.

Keywords: Radiotherapy. Chemotherapy. Adverse effects. Treatment.

Resumo

Introdução: A radioterapia (RT) e a quimioterapia (QT) são terapias amplamente empregadas em pacientes portadores de neoplasias malignas em região de cabeça e pescoço. No entanto, são métodos capazes de provocar toxicidades significativas às estruturas orais e tecidos adjacentes. **Objetivo:** Descrever as complicações bucais agudas e crônicas da RT e QT em cabeça e pescoço, evidenciando a maneira com que o cirurgião-dentista (CD) pode abordá-los. **Materiais e métodos:** Biblioteca Virtual em Saúde (BVS) – Bireme: LILACS, IBECS, MEDLINE e BBO - PubMed, SciELO, Biblioteca Digital Brasileira de Teses e Dissertações (BDTD), Base Periódicos Capes e livros renomados da área estomatológica. A estratégia de busca utilizada incluiu as seguintes palavras: radioterapia, quimioterapia, efeitos adversos e tratamento. Foram selecionadas 32 referências entre 1990 e 2012 para o desenvolvimento deste estudo. **Resultados:** Ambas as terapias estão associadas a reações adversas que afetam de forma significativa a qualidade de vida dos pacientes. Seus efeitos adversos são dose-dependentes e podem manifestar-se a partir da primeira semana de tratamento. Entre as complicações orais mais importantes estão a mucosite, radiodermite, hipossalínia, hipogeusia, cárie de radiação, infecções oportunistas, anormalidades do desenvolvimento, osteorradionecrose e trismo. A avaliação prévia da condição bucal e o acompanhamento pelo CD durante o tratamento podem atuar na prevenção e redução dos danos causados aos tecidos bucais. **Conclusão:** O tratamento multidisciplinar, incluindo equipe médica, cirurgião-dentista, fonoaudiólogo, nutricionista e psicólogo é a melhor alternativa para minimizar ou mesmo prevenir diversas complicações físicas e psicológicas advindas do tratamento antineoplásico.

Palavras-chave Radioterapia. Quimioterapia. Efeitos adversos. Tratamento.

Introduction

There are several types of cancer that can affect head and neck regions. According to the National Cancer Institute (INCA), there were 6.510 deaths caused by mouth cancer in the last 2009 survey, and there are 14.170 new cases estimated for the country in 2012 (1). The treatment of these cancers can be by surgery, radiotherapy and chemotherapy; the choice depending on location and staging of the lesion as well as the patient's condition and prognosis (2, 3, 4). No anticancer treatment currently available is apt to destroy tumor cells without harming the healthy tissue (4). Xerostomia, mucositis, muscle trismus, osteoradionecrosis, caries, opportunistic infections, dysphagia, hypogesia, dysgeusia and hyposialie are some of the oral sequelae resulting from cancer treatment (5).

The dentist is the most qualified professional to evaluate and treat oral diseases, as well as implementing preventive measures to monitor the oral health of cancer patients treated with radiotherapy

or chemotherapy, in order to minimize the stomatological and functional effects caused by these therapies, being therefore extremely important the integration of this professional with the oncology team in the care of cancer patients in all stages of the disease (6).

This study aims at demonstrating, through literature review, the impact of radiotherapy and chemotherapy in the oral cavity and associated structures, seeking to discuss the major sequelae that can occur as a result, emphasizing the importance of dental care in prevention and treatment of side effects from these therapies, thereby providing better quality of life for the patient.

Literature review

Radiotherapy (RT) is a primary or adjuvant therapeutic method that has been widely used in the treatment of malignancies of the head and neck regions, with improved patient survival (4). This

therapy can have curative intent when it aims at eliminating the cancer cells.

The chemotherapy (CT), in turn, is the use of drugs known as chemotherapeutics, which act by destroying and/or controlling the growth of diseased cells, interfering with the ability of multiplication of cancer cells. While the mucosa of healthy individuals supports the routine trauma, chemotherapy predisposes to the mucosal rupture, ulceration and secondary infections (7). Regardless of the purpose of therapy, the use of ionizing and chemotherapeutic radiation can cause significant damage to the oral structures and adjacent tissues (5).

Hyposialie and xerostomia

The hyposialie occurs by decreased salivary flow, which results in xerostomia (subclinical condition characterized by complaints of dry mouth with no proven decrease in saliva production), persistent and common complications of head and neck radiotherapy.

The salivary hypofunction is directly related to the radiation dose received and the amount of salivary gland tissue irradiated. Therefore, the higher the radiation dose, the worse the prognosis for xerostomia, with symptoms minimized through palliative conducts (4).

The residual saliva becomes viscous, with less lubricity and protection, given the reduced amount of mucin. There is also a marked decrease in pH, which makes it more acidic due to a change in the concentrations of calcium, sodium and bicarbonates (8). This change of saliva and salivary flow may contribute to the increased risk of infections of the oral tissues, bacterial plaque accumulation and the development of "radiation caries" (4, 9), impairing the chewing, swallowing, tasting and talking (9).

Patients with xerostomia may present a framework of generalized mouth burning, discomfort and even erythema at the apex of the tongue. To prevent opportunistic infections, patients should be instructed to make mouthwash with 0.2% or 0.1% chlorhexidine in aqueous solution. The daily application of fluoride should be instituted, combatting radiation caries (4).

For control of radio-induced xerostomia, the patient is advised to avoid agents that can reduce salivary flow, especially tobacco and alcohol. Mouthwashes

and frequent water intake are indicated, in addition to the use of sugarless chewing gum and artificial saliva and salivary gland stimulators, such as 2% pilocarpine, which can provide more comfort in chewing and swallowing (4). In some patients, pilocarpine hydrochloride has been effective in stimulating the production of saliva; however, it is only efficient if the gland presents some residual function (10). Foods rich in ascorbic, malic or citric acid will stimulate the glands, increasing salivary flow, but the acidity can cause injury to oral tissues, aggravate mucositis and contribute to teeth demineralization (11).

The patient's irradiated salivary function tends to return in two to six months, or even one year after therapy completion; however, particularly when the parotid glands are involved, the impairment may be irreversible (8).

Fungal infections

The *Candida albicans* is the most common microorganism in oral infections of patients undergoing anticancer treatment. The lesions on the oral mucosa caused by *C. albicans* can appear as detachable white plates, which leave a reddish base after removed.

The management of patients includes frequent mouthwash with chlorhexidine and topical antifungals such as ketoconazole and nystatin (12). Chlorhexidine should be used at least 30 minutes before or after use of any antifungal in order to be effective.

Viral infections

Viral infections with oral manifestations or perioral tissue are frequent complications of cancer treatment. The immunosuppression state of these patients eases to installation of opportunistic infections (13). The susceptibility of a patient to infections depends on how low the white blood cell counts are and how long they remain low.

The acquisition or infection reactivation by the herpes simplex virus (HSV) in HSV-seropositive patients is one of the most prevalent viral complications in this group of individuals during myelosuppression (13, 14). The most common locations of emergence for HSV lesions are lip vermillion border and perioral skin. The HSV, however, can also be

manifested in the oral mucosa, generally limited to keratinized mucosa.

The most common signs and symptoms of HSV infection are pain, burning, itching, located heat or redness in the epithelium involved. The lesions begin as small erythematous papules, forming vesicles that rupture, resulting in ulcerated lesion (4) and they are treated with acyclovir cream, compressed, or lyophilized powder for infusion (14).

Bacterial infections

The hyposalivation promotes breakage of homeostasis, favoring a highly significant alteration of the oral microbial flora, causing the appearance of infections and increased proliferation of microorganisms. There is primarily the exchange of non-cariogenic for cariogenic microorganisms, with predominant increase of *Lactobacilli* and *Streptococcus mutans*. Furthermore, the population of *Actinomyces naeslundii* and *Porphyromonas gingivalis*, associated with periodontal disease and root caries, is also increased after irradiation (15, 16). For these factors, the study highlights the importance of controlling bacterial plaque through proper oral hygiene.

Radiation caries

The radiation caries is not a direct effect of radiation, but secondary to hyposalivation and xerostomia. It may develop from three weeks to one year after radiation treatment, characterized by rapid and early progression, usually in the tooth cervical region. Its speed of development is far superior to conventional dental caries, since it can attain the dentin within a month, while in non-irradiated patients, the progression of dental caries takes a year, on average (8).

Besides the direct effects on the teeth, radiotherapy acts indirectly by increasing susceptibility to caries through decreased salivary flow, changing the chemical composition of saliva and development of cariogenic microorganisms.

The hyposalivation is always accompanied by a change in eating habits, and frequent consumption of soft foods rich in carbohydrates, which contributes further to the development of cavities (8).

If the injury is established, its removal and restoration should be carried out immediately, given its rapid progression. If the caries has already destroyed the entire crown and committed the pulp, the root canal treatment with obliteration of the canal should be performed, leaving the root "buried" in the alveolus. Thus, the endodontic treatment is important because it controls the painful symptomatology and provides further aesthetic and functional restoration of teeth, besides preventing osteoradionecrosis, by avoiding tooth extractions (17).

Oral hygiene should be quite accurate, including home care and regular visits to the dentist for examination and prophylaxis. Fluorine daily topical applications, both in solution form for rinsing and as neutral gel (1% sodium fluoride), are highly effective in preventing the development of caries.

Periodontal disease

The periodontal ligament is also sensitive to the effects of radiation, and blood vessels of the periodontium and periosteum are affected. Radiographically, changes in the alveolus, with the widening of the periodontal ligament space and trabecular bone destruction, can be observed. These changes increase the risk of periodontal disease, as there is reduction in the ability to repairing and remodeling (15).

Therefore, orientation in oral hygiene, as well as procedures for scaling and root planning, are essential and should be preferably introduced before radiotherapy.

Developmental abnormalities

The chemotherapy, when administered in the odontogenesis phase, can cause changes in the formation and development of tooth germs as root shortening in premolars, conoid roots in molars, premolars and canines, agenesis, microdontia, changes in root formation, hypoplasia and enamel hypocalcification.

The radiation treatment, when performed in children, from birth to puberty, may cause changes in bone growth, causing craniofacial skeletal abnormalities (maxillary or mandibular hypodevelopment) and teeth development (18).

Mucositis

Mucositis is one of the most frequent and early side effects arising from cancer treatment. Characterized by an inflammatory condition of the oral mucosa (19), the mucositis caused by chemotherapy usually involves non-keratinized surfaces, while the mucositis from radiotherapy affects the mucosal surface, facing directly the focus of radiation. Regardless of the causal therapy, the manifestation is similar, with no significant differences concerning clinical presentation (4).

The demonstration begins as redness and edematous mucosa can be found. Then, tissue atrophy may occur, such as moist desquamation, formation of erythemas, hyperkeratinization, ulceration and mucosal necrosis (1). The effects of mucositis only regress after radiation, leaving no sequelae. The period of manifestation of the erythema phase is quite varied. In chemotherapy, usually between four and five days post drug infusion; in radiotherapy, for head and neck, the first symptoms begin to appear from cumulative doses of 10 Gy, which usually happens in the second week of treatment (20).

The pain associated with mucositis depends on the degree of tissue damage, the sensitivity of nerve receptors and the production of inflammatory mediators and pain (21). Some authors admit that mucositis is more severe in patients with bad oral hygiene. In such cases, the action of viruses, fungi and opportunistic bacteria further aggravate the damage to the mucosa, increasing the risk of pain and necrosis.

Other factors that influence the severity of mucositis is the dose of radiation, dose and type of chemotherapy drugs, the patient's general condition and the use of local irritants, such as alcohol, tobacco and spicy foods (22).

Initially, the patient complains of burning, heat, swelling, pain to feed and, with the aggravation, unremitting pain, which persists during the course of therapy and several weeks later (2), slowly disappearing between two and three weeks after end of treatment (4).

Many substances have been tested for prevention and treatment of oral mucositis, such as steroids, vitamin E and oral supplementation with glutamine (23, 24). As palliative treatment, there is the use of topical analgesics, mouthwashes containing chlorhexidine to reduce the risk of infection, mouth rinses with benzylamine hydrochloride to reduce pain or systemic analgesics (12).

The use of low-level laser therapy has been proven effective in controlling symptoms of mucositis, promoting the release of prostaglandins, thus having an anti-inflammatory action. It also promotes the release of endorphins, helping to control pain (19). The use of therapeutic protocol with the low-power InGaAIP laser was suggested before and, during radiotherapy, should be performed daily with 35 mW of power and a 1.1 J/cm² energy dose (19). However, more controlled scientific studies are needed, aiming at developing a protocol for this therapeutic modality.

Hypogeusia and dysgeusia

The hypogeusia is defined as the reduction or loss of the four tastes and can be observed after two weeks of radiotherapy. It occurs because taste buds are very sensitive to radiation, mainly the circumvallate and fungiform papillae, reason why patients may develop partial or complete loss of taste during treatment. Associated with pain, dysphagia, hyposalivation and depression, it generates loss of feeding pleasure, loss of appetite and malnutrition (15). The hypogeusia can be permanent and some individuals can also exhibit dysgeusia.

As a means of prevention and treatment, patients with this complaint may be supplemented with zinc and copper (25).

Muscle Trismus

The trismus of masticatory muscles is characterized by contraction of the masseter muscle, resulting in difficulty in mouth opening (9). This makes it difficult to clean, and some may develop or intensify adverse oral effects of anticancer therapy (13). It is a relatively common complication after radiation of head and neck, resulting from hypovascularization, edema, cellular destruction, atrophy and fibrosis of the muscle tissue affected by radiation (26).

The prevention and treatment of trismus consist of physiotherapy sessions that should vary with the level of the patient's involvement (26). The study suggests that patients with head and neck cancer without physiotherapy intervention present constraint of mandibular movements during the radiotherapy treatment, indicating that

this complication should be assessed during the radiotherapy course, especially if the patient has reduced functional capacity, irradiation for mouth and oropharyngeal fields and make use of nasoenteric probe (27).

Clinical studies on the treatment of trismus with low-power laser have revealed a significant increase of mouth opening in patients irradiated immediately after application (28, 29). However, a low-level laser therapy does not replace traditional treatments and may be associated with conventional therapies, promoting better clinical resolution (9).

Radiodermatitis

Characterized by a skin reaction potentially painful resulting from radiotherapy. The moderate radiation, with the progression of applications, causes erythema and swelling, which may or may not be followed by peeling ulceration (30).

The acute dermatitis in the fields of radiation is common and varies with the intensity of the treatment. The chronic dermatitis is characterized by bright areas, atrophic, necrotic, telangiectatic, ulcerated or plucked (4).

Osteoradionecrosis

Osteoradionecrosis is one of the most severe and undesirable complications resulting from radiotherapy of head and neck (3, 8). Its pathogenesis is related to the formation of a hypoxic-hypocellular-hypovascular tissue resulting from irradiation, with consequent disruption of the oral mucosal barrier, spontaneously or traumatic, resulting in non-healing process. The bone cells and vascularization may show irreversible damage and, in many cases, devitalized bone fragments can generate bone sequesters (31).

The anatomic site most commonly affected is the jaw, by showing a more compact and dense bone structure, lower intake and blood flow compared to the maxilla. Clinically, it is characterized by the exposure of necrotic bone, that may be associated with signs and symptoms such as intractable pain, cortical perforation, fistula formation, superficial ulceration and pathological fracture, not always associated with infection. Radiographically, it is a bad-defined radiolucent

image without sclerotic borders. When there are bones' sequester, radiopaque images can exist (18).

The treatment consists of surgery, wound cleaning and debridement, antibiotics and hyperbaric oxygenation. To perform extractions after radiotherapy, a number of conservative measures should be adopted: preventing removal of surrounding bone and minimum mucoperiosteal displacement and alveoplasty, as well as good suturing must be performed to allow the first-intention repair.

Teeth in poor condition, bone trauma, periodontal disease, combined chemotherapy (systemic immunosuppression) and extractions are risk factors for osteoradionecrosis and therefore should be avoided (8).

Neurotoxicity

Neurotoxicity is characterized by non-specific pain, persistent and continuous, which can be caused by some chemotherapy agents promoting changes in nerves of the head and neck, depending on the dosage and duration of its administration. Though a rare complication, it is of great relevance to dentistry, as the pain from the neurotoxicity is similar to the pulpitis pain. Symptoms appear and disappear spontaneously, which makes the diagnosis difficult. Dental or mucosal changes are not seen and the thickening of the periodontal ligament in vital teeth can be observed by the radiographic examination (5, 14). The treatment of neurotoxicity must be met through the administration of systemic analgesics and, by stopping the chemotherapeutic drug, symptoms often disappear.

Oral assessment protocol

There is a wide range of therapeutic and prophylactic conducts described in the literature to address the cancer patient. There is an oral assessment protocol pre-anticancer therapy, which is able to identify the risk factors for the development of predictable oral complications; therefore the preparation and guidance previously provided are able to reduce them (7). To elucidate the basic protocol for dental treatment of the patient under anticancer treatment, two tables were prepared (Tables 1 and 2).

Table 1 - Clinical protocol for prevention and oral treatment of radiotherapy patients

Dental treatment of cancer patients
Oral hygiene instructions
Diet orientation (minimum intake of sucrose)
Prophylaxis
Scaling and root planing
Prescription of mouthwashes with fluoride solutions
Manufacturing of individual trays for topical application of 1.23% acidulated phosphate fluoride gel
Prescription of neutral fluoride gel for daily use in trays
Elimination of active caries
Elimination of potential sources of irritation (acute cusps, fractured, orthodontic bands, poorly fitted dentures and broken hairpins)
Frequent examination and prophylaxis (every six or eight weeks)
Keep the protocol for 12 months after radiotherapy

Source: Research data.

Table 2 - Oral manifestations and possible therapeutic approaches for cancer patients undergoing chemotherapy or radiotherapy for head and neck

(Continua)

Therapeutic approach: oral complications resulting from oncological treatment of head and neck			
Changes	Medication	Dosage	Approach
Mucositis	0.12% chlorhexidine (12, 15)	Topical	
	Painkillers (12)	Oral	
	Low level laser therapy (19)	Red laser /infra-red. E = 0.7J to 4J. T = 10 to 300 seconds. Daily application, punctual.	Before and during chemotherapy or radiotherapy
Oral infections fungal	Nystatin (12)	Topical	From the early infectious manifestation
	Antifungals (12)	Oral	
Oral infections viral	0.12% chlorhexidine (15)	Topical	Before and during chemotherapy or radiotherapy
	Acyclovir (14)	Topical (cream) Oral Infusion (lyophilized powder)	From the early infectious manifestation
	Antibiotics (15)	Topical Oral	From the early infectious manifestation
Oral infections bacterial			
Changes in glandular functions(xerostomia, radiation caries)	Chewing sugarless gum (11)	Topical	
	Pilocarpine 2% (4, 10)		From the detection of alterations in glandular function
	Artificial saliva (4)		
Osteoradionecrosis	Surgery intervention (8)	Debridement and removal of the necrotic bone	When there is emergence of bone sequestration
Periodontal disease	Guidance on oral hygiene (15)		
	Removal of retentive factors of bacterial biofilms (15)	According to the dentist decision	Throughout the anticancer treatment
Hypoguesia	Guidance and monitoring (15)	According to the professional decision	From the early manifestation of hypoguesia

Table 2 - Oral manifestations and possible therapeutic approaches for cancer patients undergoing chemotherapy or radiotherapy for head and neck

(Conclusão)

Therapeutic approach: oral complications resulting from oncological treatment of head and neck			
Changes	Medication	Dosage	Approach
Muscular trismus	NSAIDs (32) Muscle relaxant (32)	Oral	
	Low level laser therapy (9, 28, 29)	Red laser /infra-red. E = 1J to 3J. T = 120-350 seconds. Applied to the musculature	Treatment should be started from the manifestation of muscle trismus
	Physiotherapy (26)	According to the professional decision	

Source: Research data.

Conclusions

The antineoplastic therapies currently available are capable of causing significant toxicities to the oral structures and adjacent tissues. Its adverse effects may manifest starting from the first week of treatment, given the indisputable knowledge of dentists about these events, which significantly affect the life quality of patients.

Prevention is still the best approach, with regard to secondary sequelae to the chemotherapy; therefore, the inclusion of dentists in an oncology team is crucial, once this professional should prepare the patient for anticancer treatment, as well as accompanying him during therapy, providing better oral hygiene and quality of life.

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