Review Article
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Review of Oral and Dental Consideration in the Patients with Head and Neck Radiotherapy and Chemotherapy

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Objectives Aggressive cancer therapy places patients at a greater risk for oral complications. Cancer patients suffer from oral toxic effects secondary to antineoplastic therapy (radiotherapy and chemotherapy). The aim of this review is management of the head and neck cancer patients that specifically emphasizes the prevention and treatment of oral and dental complications associated with cancer therapy.

Methods In this narrative review article, the specialized databases such as PubMed, PubMed Central, MEDLINE, EBSCO, Science Direct, Scopus from 2008 to 2018 were used to find relevant documents by using Mesh terms: Chemotherapy, Radiotherapy, oral consideration, head and neck.

Results The data were categorized in: Complications of head and neck radiotherapy and its management (Xerostomia, Oral Infection, Oral Mucositis, Osteoradionecrosis), Complications of head and neck chemotherapy and its management (Mucosal toxicity, Dental alterations, Neurological disorders, Salivary alterations, Dysgeusia, Infections, Bleeding tendency, Osteonecrosis of the jaws due to bisphosphonates).

Conclusion In order to minimize morbidity in the head and neck cancer patients, it is recommended for consulting to dental health care providers before, during and after cancer therapy.

Keywords Chemotherapy, Radiotherapy, Management, Head and neck neoplasm

Introduction

Acute and chronic reactions occur during the course of radiotherapy and chemotherapy. Pretreatment diagnosis and treatment is critical in preventing the serious squeal of cancer therapy and improving the patient's quality of life[1]. A thorough oral examination is recommended, comprising an evaluation of the dentition and surrounding supportive periodontium, and a complete radiographic survey conducted as early in the course of treatment as possible. During this examination, hopeless and non-restorable teeth must be removed before treatment to minimize the risk for the development of complications, such as odontogenic facial abscesses and osteoradionecrosis[2, 3]. The early recognition of opportunistic infections, such as candidiasis or herpetic infections and their management also will improve the patient's overall health[4]. Communication between the physician and dentist must be established and continued throughout the patient's course of treatment. The dentist must have an understanding of the patient's medical history, diagnosis, staging, and planned therapy to develop an appropriate treatment plan[5]. Additionally, performing oral surgery on an immunosuppressed patient who has thrombocytopenia and neutropenia may result in serious complications not foreseen by the treating dentist [2, 5]. Dental decay may progress to the vital pulpal tissues of the tooth, leading to an increase in pain and sensitivity and often causing necrosis of the vital pulp and the formation of an abscess[6]. The abscessed pulpal tissues may not present with symptoms and may spread rapidly to involve the fascial planes of the head and neck region, resulting in space infections or extensions beyond the head and neck region[6, 7]. These infections may prove life-threatening and difficult to manage in the immunocompromised patient[6]. The dentist plays a critical role in the multidisciplinary approach to treating the head and neck cancer patients[8, 9]. The dental examination should include a detailed clinical examination with a full-mouth radiographic survey to ensure that all dental disease is revealed[9].

Complications of head and neck radiotherapy and its management

The oral tissues directly affected by head and neck radiation therapy include the mucosal membranes, the salivary glands, the jaw muscles and bone[10-13]. Dry mouth (xerostomia) is a common and significant consequence of head and neck radiotherapy. patients with xerostomia are more susceptible to rampant caries, periodontal disease and oral fungal and bacterial infections[14]. Mucositis, characterized by inflammation and ulceration of the oral mucosa, is the most significant acute side effect reported by patients and is a potential source of life-threatening infection[14]. Almost all patients undergoing head and neck

radiation therapy experience mucositis approximately the third week of treatment[14, 15]. Also radiotherapy can induce fibrosis around the muscles of mastication, leading to trismus. It is believed that jaw exercises may limit the severity of trismus, but they will not mobilize fibrosis once it has occurred[16]. Bone exposed to high levels of radiation undergoes irreversible physiologic changes including narrowing of the vascular channels (endarteritis), which diminishes blood flow to the area, and loss of osteocytes. The bone essentially becomes nonvital, which leads to limited remodeling of bone and limited healing potential .(osteoradionecrosis)[17].

1.1. Xerostomia

Xerostomia is a common and significant consequence of head and neck radiotherapy.

Systemic sialagogues increase the production of saliva from functional glands. There is no optimal substitute for saliva. Pilocarpine (Salagen) and Cevimeline (Evoxac) have shown promising effects in increasing saliva but is only effective for salivary glands with residual function[18 , 19.] Two alternative medications that may be beneficial in stimulating salivary glands include anethole trithione (Sialor) and bethanechol (Urecholine)[20]. Although saliva replacements such as UniMist (Westons Health), Mouth Kote (Parnell Pharmaceuticals) and Oral Balance Gel (Laclede Pharmaceuticals) are poor salivary substitutes, as they primarily attempt to mimic the texture of saliva but do not simulate the rheologic properties. Oral Balance Gel may be the best accepted by patients because of its extended duration of effect. Sugarless gum or lozenges may stimulate salivary secretion in patients with residual salivary gland function[18]. Sugar-free popsicles, plain ice cubes or ice water may be used to keep the mouth cool and moist. Eating foods high in ascorbic acid, malic acid or citric acid will stimulate the glands to increase salivary flow, but this measure is not recommended in dentate patients because the acidity can further irritate oral tissues and contribute to the demineralization of teeth[18]. For the prevention of rampant dental demineralization and caries, patients should apply a 1.1% neutral sodium fluoride gel daily (for at least 5 minutes), using a custom fitted vinyl tray if possible[9]. This protocol may be started on the first day of radiation therapy and continued daily as long as salivary flow rates are low. High-potency fluoride brush-on gels and dentifrices may be considered in those who are unable or unwilling to comply with the use of fluoride trays[8].

1.2. Oral Infection

Health care providers should be concerned about infections in cancer patients. A fungal, bacterial or viral culture is recommended if infection is suspected[4, 21]. In patients undergoing head and neck radiotherapy, Candida colonization tends to increase throughout the course of treatment and remains increased if xerostomia occurs[4]. Nystatin rinses are the most widely prescribed treatment for oral fungal infections, despite a lack of proven efficacy. Nystatin has an unpleasant flavor and may cause nausea and vomiting[4], and its high sucrose content is a major concern in dentate patients. For more severe infections, the use of a systemic antifungal medication such as fluconazole (Diflucan) or amphotericin B is recommended. Systemic amphotericin B must be used with caution because of its potential to cause liver toxicity[22]. Topical antifungals to consider include clotrimazole, ketoconazole and chlorhexidine. Chlorhexidine gluconate 0.12%; (Peridex), an antimicrobial rinse, has both antifungal and antibacterial properties in addition to antiplaque effects; however, its value is still unconfirmed. Its tendency to stain teeth and its alcohol content, which can irritate inflamed tissues, are drawbacks[22]. If chlorhexidine is used, it is important to note that nystatin and chlorhexidine should not be used concurrently, because chlorhexidine binds to nystatin, rendering both ineffective [22], furthermore, chlorhexidine should be used at least 30 minutes before or after the use of any other topical agents with which it may bind.

For cancer patients with viral infections, such as Herpes simplex 1, acyclovir (Zovirax, GlaxoSmithKline) or derivatives are recommended for both prophylaxis and treatment[21, 23]. Pencyclovir (Denavir, GlaxoSmithKline), a newer topical antiviral with increased tissue penetration, is now available[17.]

1.3. Oral Mucositis

Mucositis, characterized by inflammation and ulceration of the oral mucosa, and is the most significant acute side effect of radiotherapy. The use of a common oral rinse[24], is often suggested, but no studies have confirmed any beneficial effect upon mucositis. It has been suggested that patients begin prophylactic rinses with chlorhexidine to prevent the onset of microbial infection, gum inflammation and bleeding, and to reduce the risk of caries. While some authors report that a chlorhexidine oral rinse has potential effects on mucositis, others report no effects have been reported for radiation induced mucositis to date[25]. Use of other oral rinses, including commercial alcohol-based mouthwashes and hydrogen peroxide rinses, should be discontinued because of their drying and irritating effects on the oral mucosa[25]. The discomfort of mucositis can be reduced with coating agents, topical anesthetics and analgesics, although systemic analgesics are frequently needed[14]. Aluminum hydroxide/magnesium hydroxide (milk of magnesia-Maalox) and sucralfate have been suggested as coating agents for the oral mucosa. Sucralfate

suspension may also be helpful in the treatment of oral pain, although the effect on mucositis has not been clearly documented[26]. Topical anesthetics used in rinse form may result in intense but short-term anesthesia. However, the localized anesthesia can increase the risk of aspiration, and their systemic absorption can cause cardiac effects[27]. When oral mucosal pain is present, benzydamine hydrochloride (Tantum), doxepin suspension 0.5% or an antihistamine such as diphenhydramine can be prescribed[27]. Benzydamine is the only medication available that has been shown in multicentre, double-blind controlled studies to reduce mucositis and pain in patients with head and neck cancer[28]. Topical anesthetics, such as benzocaine, viscous lidocaine and topical benzocaine can be applied locally to sites of pain with a swab or a soft vinyl mouth guard[29]. Of all available mouth rinses that can be used as treatments for mucositis, the least costly and easiest for patients to prepare is a simple mouthwash comprising a teaspoon (10 mL) of salt and a teaspoon (10 mL) of baking soda (sodium bicarbonate) in 8 ounces (250 mL) of water. A comparison among salt and soda mouthwashes, mouthwashes prepared from lidocaine and diphenhydramine with Maalox, and mouthwashes of 0.12% chlorhexidine gluconate found that the 3 options were equally effective in the treatment of chemotherapy-induced mucositis[29].

1.4. Osteoradionecrosis

Osteoradionecrosis (ORN) is irreversible, progressive devitalization of irradiated bone. The condition is characterized by necrotic tissue and bone that fails to heal spontaneously. Most cases of ORN occur in the mandible, where vascularization is poor and bone density is high[30]. Clinical manifestations of ORN may include pain, exposed necrotic bone, orofacial fistulas, pathologic fracture and suppuration[30]. One-third of ORN cases occur spontaneously. Many cases with ORN have been initiated by trauma from extraction of teeth. The incidence of ORN is twice as high in dentate patients as it is among edentulous patients. Poor oral hygiene and use of tobacco and alcohol may also lead to rapid onset of ORN. It is optimal to allow 14 to 21 days for healing of the alveolar bone before beginning radiation therapy .10 Over the years, ORN has been treated by numerous methods with variable success[31]. Hyperbaric oxygen therapy is an adjunctive treatment for ORN, often used in conjunction with surgery, and has been associated with better success rates than surgery alone[32].

2. Complications of head and neck chemotherapy and its management

The oral complications of chemotherapy are either a result of direct action of the drug upon the oral mucosa, or an indirect consequence of chemotherapeutic drug-induced bone marrow suppression or myelo suppression[33].

2.1. Mucosal toxicity

The cells of the oral cavity have a fast turnover rate, with a cycle of 7-14 days. This explains the special susceptibility of the oral mucosa to the toxic effects of cytotoxic drugs[34, 35]. Mucositis manifests as reddening (erythema), edema or ulceration that can be accompanied by a mild burning sensation. Extreme presentations in turn are characterized by large and painful ulcers that have a strong impact upon patient quality of life – limiting basic functions such as speech, eating or the swallowing saliva. Mucositis can often become over-infected, mainly with herpes simplex virus or Candida albicans, particularly in patients with prolonged neutropenia. Correct oral hygiene and a good gingival condition during chemotherapy are associated to a lesser incidence and severity of mucositis[35]. About using of drugs or substances for the prevention and treatment of mucositis, the literature offers contradictory information[35]. Good results have been reported with the application of ice before and during chemotherapy[36], and also with the use of ise-ganan HCl[37]. Other treatment such as palifermin[38], granulocyte colony stimulating factor (G-CSF), oral glutamine, and macrophages in rinses, the topical application of polyvinylpyrrolidone (PVP) and hyaluronic acid[39], and low-intensity laser phototherapy, have been related to a decrease in the appearance and severity of mucositis[40].

2.2. Dental alterations

Chemotherapy can cause a range of aesthetic and functional dental problems, mostly in children treated before 5 years of age. However, prepubertal children are also at risk of suffering such late effects in contrast to radiotherapy, which only affects the cells of the irradiated zone, chemotherapy exerts a systemic effect. Due to the short half-life of cytostatic drugs, the dental defects are generally localized, and are secondary to transient changes in odontoblast function, rather than apoptosis.

The shape and size of the crown in the temporal dentition are not affected, since crown morphology is determined before birth. However, in the case of the permanent dentition, we can observe macrodontia with a prevalence of 2.2-5.2%, due to the action of certain chemotherapeutic drugs such as vinblastine and vincristine upon the mature odontoblasts and ameloblasts[41]. Chemotherapy also causes morphological anomalies of the dental roots. In this context, in children under 5 years of age we can observe alterations of the roots of the upper and lower premolars, while older children show alterations of the roots of the upper and lower

molars, premolars and canines[42, 43]. The action of cytostatic drugs upon the microtubules of the odontoblasts interrupts the formation of collagen fibrils and dentinal matrix secretion, giving rise to thin and sharp-pointed roots. Also chemotherapy causes agenesis hypodontia and hypoplasia[43].

Some authors have described an increased incidence of caries in children subjected to chemotherapy, though the data are controversial, since caries may result from an increased use of rinses, often with a high sugar content, to treat hypo salivation[44]. In adults, a number of studies have reported an increase in caries in patients subjected to chemotherapy. Children scheduled for chemotherapy should undergo a thorough clinical and radiological evaluation by the dentist[44]. Periodic follow up should be made, every 6 months. The recommended tooth brushing frequency varies, though at least two daily brushings are advised, using fluorated toothpaste. Chlorhexidine varnish also can be applied twice a day as a preventive measure against caries[44].

2.3. Neurological Pain

Neurotoxicity accounts for 6% of all oral complications, causing pain similar to pulpitis and discomfort. The pain sensation is constant and of sudden onset, affecting the region of the lower molars in the absence of dental disease. An oral and radiological exploration should be made to distinguish the pain from that of pulp origin. The symptoms usually disappear one week after chemotherapy. In some cases dental hypersensitivity can manifest weeks or months later. In these cases topical fluoride or the use of a desensitizing toothpaste may lessen the symptoms[45].

2.4. Salivary alterations

- Salivary immunoglobulin and PH

Chemotherapy decreases the salivary production of immunoglobulins also affects a series of salivary components, such as immunoglobulins, amylases, peroxidases and other proteins[46]. Decreasing in IgG and IgA could explain some of the oral complications of chemotherapy. Decrease in IgA has been associated to the appearance of mucositis in patients receiving chemotherapy.

Some authors have reported a modification in salivary buffer capacity after the administration of chemotherapy[46]. However, other investigators have observed no significant variations following the administration of cytostatic agents.

- Xerostomia

Chemotherapy can give rise to a temporary but clinically significant decrease in salivary flow that improves as the bone marrow recovers[20]. Such a decrease in salivary flow in turn favors the appearance of mucositis[19]. The symptoms of xerostomia or dry mouth include dryness, burning sensation or discomfort (particularly of the tongue), cracked lips, changes in the tongue surface, and problems in wearing removable dentures or drinking liquids[18]. The condition tends to be preceded by a metallic taste sensation that subsequently can lead to dysgeusia and glossodynia secondary to the effects of chemotherapy upon the tongue papillae and demineralization of the nerve fibers[18, 20].

In treating xerostomia it is advisable to maintain adequate oral hydration by means of the regular intake of water, the use of saliva substitutes or cholinergic agonists such as pilocarpine, cevimeline or bethanechol (when pilocarpine proves ineffective); these measures moreover favor integrity of the oral mucosa[18].

2.5. Dysgeusia

The main cause of dysgeusia in cancer patients is the action of radiotherapy and chemotherapy upon oral epithelial cell turnover, and the effects of such treatments upon nerves, taste buds and olfactory receptors[47]. The patients present distorted taste sensation, describing a metallic or very salty taste of food. These situations can adversely affect patient food intake and nutritional condition. Although dysgeusia has multiple origins, there are simple forms of treatment, such as a reduction of the dose of certain chemotherapeutic drugs (e.g., histone deacetylase inhibitors), the treatment of oral infections, and dietetic counseling[48]. In relation to this latter aspect, it is advisable to increase liquid intake with meals, and chew food slowly - thereby freeing more flavors and especially increasing saliva production. In addition, diversity during meals is advisable, in order to prevent taste bud adaptation to flavors. Other pharmacological strategies include zinc supplements and amifostine .However, the results obtained in different clinical trials have not been entirely satisfactory, and other treatment alternatives, such as vitamin D supplements, are therefore being investigated[48].

2.6. Infections

Cytostatic agents can affect the bone marrow, producing anemia, leukopenia and thrombopenia. As a result of their indirect toxicity mechanism, the oral cavity becomes more vulnerable to infections approximately one week following the administration of these drugs. Bone marrow function must be evaluated, since the reduction or absence of inflammatory phenomena causes the oral tissues to appear normal; infections therefore go unnoticed, and septicemia may result. It should be noted that apart from causing frequent infections, agranulocytosis also produces neutropenic ulcers, which are characterized by a central necrotic area, no perilesional erythematous halo, and irregular margins[49]. These ulcerations are generally large and painful and may be covered by a fibrin membrane.

They appear in both keratinized and non-keratinized tissues and are associated with granulocyte counts of under 800 cells/μl[49].

2.7. Bleeding Tendency

Bleeding tendency in the oral cavity usually appears after trauma during chewing in patients with pre-existing periodontal disease- especially patients with prior gingivitis and a platelet count of less than 20,000 platelets/mm^3. Clinically, we can observe petechiae, ecchymosis, and hematomas or diffuse bleeding in any location of the oral cavity. Oral rinses with 0.12% chlorhexidine avoid over infection and can help eliminate remaining blood, though caution is required not to disturb the blood clots, since this may lead to further bleeding[50]. The treatment of choice in cases of bleeding consists of vasoconstrictors such as topical norepinephrine, mucoadherent tissue protectors such as cyanoacrylate, and coagulation-favoring drugs such as topical thrombin or hemostatic collagen, which organize and stabilize the blood clots[50]. In individuals subjected to chemotherapy who require invasive dental treatment, the hematological condition of the patient must be taken into account, with consultation of the supervising oncologist. In the presence of a platelet count of under 50,000 platelets/mm3, it is advisable to provide invasive dental treatment in the hospital setting, following transfusion assessment.

2.8. Osteonecrosis of the jaws

Bisphosphonates (BPs) are potent inhibitors of osteoclastic bone reabsorption and have been used for decades for the treatment of osteoporosis, malignant hypercalcemia, bone metastases and myeloma. The development of osteonecrosis of the jaws (ONJ) has been associated to a number of general risk factors, such as the type of BP administered, the duration of treatment, the type of neoplasm, the existence of concomitant treatments (chemotherapy, head and neck radiotherapy, corticosteroids, thalidomide or bortezomib), and the presence of other disease conditions (anemia, diabetes, obesity, hypercalcemia and coagulation disorders)[51]. Local risk factors in turn include dentoalveolar surgery, the mandibular location, bone protuberances (torus, mylohyoid crest) and concomitant oral disease (periodontal or dental infections)[51]. Other contributing cofactors are alcohol, smoking, deficient oral hygiene, obesity and old age. Clinically, the onset of ONJ can be nonspecific. The patient may describe discomfort around a tooth, a lack of healing after tooth extraction, or ulceration of the oral mucosa[52, 53]. As the lesions advance, the patient may develop pain, exposure of necrotic bone, fistulization, purulent secretion, alveolar nerve paresthesia, dental mobility, involvement of the maxillary sinus, and mandibular fracture[54]. If the patient is receiving treatment with BPs, it is advisable to evaluate the oral cavity every 6-12 months. The treatment of ONJ is controversial, and no effective or fully consensus-based guidelines have been established, though a number of management strategies have been used, such as the interruption of BPs, surgical treatment, the use of hyperbaric oxygen, and the application of ozone, laser surgery, or low-intensity laser therapy .Research is still being conducted on the efficacy of the treatment of ONJ with pentoxyphylline, α-tocopherol or teriparatide. Most authors agree that conservative management of ONJ is the best approach[55], since mucosal healing can be achieved in at least 23-53% of all patients by adopting less aggressive treatments.

Conclusion

Radiotherapy and chemotherapy have been used in the head and neck cancer treatment. However, these therapies can cause several adverse reactions that affect quality of life in the patients, it is very important that health care providers are familiarized with these complications that may result from anti-neoplastic therapies. Multidisciplinary treatment, including medical team, oral care providers, nutritionists and psychologists, is the best option in order to minimize or even prevent such complications.

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Conflict of Interests

None Declared ■

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