

Oral Changes in Patients Undergoing Chemotherapy

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Abstract: Cancer is a class of disease characterized by out of control cell growth. It is also common term for neoplasm, or tumors that are malignant. All cancer is caused by the malfunction of genes that control cell growth, division and maturation. Chemotherapy is responsible for the long term survival of patient with malignancies. Chemotherapeutic regimens have deleterious effect on both normal cells and tumor cells. Certain normal cell such as those oral mucosa divide rapidly. Thus, the effect of chemotherapy may results in oral complication such as mucositis, xerostomia, osteoradionecrosis and etc. These complications have a negative impact upon patients quality of life and it may life threatening in some case.

Introduction

Cancer also known as a malignant tumor or malignant neoplasm is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The etiology of cancer can be grouped into both external factors and internal factors. External factors include tobacco, alcohol, chemicals, solar and ionizing radiation, infectious microorganisms, environmental pollutants, medications, and even nutrients. Internal factors include inherited mutations, hormones, immune conditions, and mutations occurring from errors in metabolism. All of these factors may act synergistically or in sequence to initiate the process of carcinogenesis. All cancer is caused by the malfunction of genes that control cell growth, division, and maturation. Chemotherapy are the most widely used interventions for the treatment of cancer. Despite the advances in cancer management, chemotherapy remains one of the most commonly used treatment modalities, either alone or in combination with other types of treatment. The great inconvenience of chemotherapy is its lack of selectivity, since it acts upon both tumor cells and rapidly multiplying normal cells (1). Although these treatment are employed to improve the patient's quality of life, they are associated with several side effects. Up to 40% of all patients receiving cancer chemotherapy develop acute oral complications. (2) Oral complications that arise with chemotherapy include mucositis, xerostomia (dry mouth), bacterial, fungal, dental caries, dysgeusia and osteoradionecrosis. (3) The oral cavity is very susceptible to the direct and indirect toxic effects of chemotherapy. This is due to a number of factors, including the high cellular turnover rate of the oral mucosa, the complex and diverse microflora of the oral cavity, and oral tissue trauma occurring during normal oral function. (4) It is therefore essential to evaluate the oral condition of the patient and to stabilize any oral disease conditions before cancer treatment is provided. (5)

Mucositis

Mucositis is a common dose-limiting complication in patients receiving systemic anticancer chemotherapy, bone marrow transplantation, and local irradiation for tumors in the head and neck area. (6) Incidence as well as severity may vary from patient to patient. The probability of developing mucositis is dependent upon the treatment. It is estimated that about 40% of patients treated with standard chemotherapy develop mucositis. (2) The risk of developing mucosal injury increases with the number of chemotherapy cycles and previous episodes of chemotherapy-induced mucositis. (6) The degree and duration of mucositis in patients treated with chemotherapy are related to radiation source, cumulative dose, dose intensity, volume of radiated mucosa, smoking, alcohol consumption, and oral hygiene. (7) Within the oral cavity, the non-keratinized areas such as the buccal mucosa, floor of mouth, ventral tongue, and soft palate are the most commonly affected sites. (9) Mucositis develops in 4 phases: initiation, message

generation, signal amplification, ulceration, and healing phase. Phase I: Initial inflammatory/vascular phase. During this phase, exposed cells (epithelial, endothelial, and connective tissue cells) in the buccal mucosa release free radicals, modified proteins, and proinflammatory cytokines, including interleukin-1B, prostaglandins, and tumor necrosis factor (TNF). These inflammatory mediators cause further damage either directly or indirectly by increasing vascular permeability, thereby enhancing cytotoxic drug uptake into the oral mucosa (10). Phase II: Epithelial phase: In this phase, chemotherapy and/or radiation retards cell division in the oral mucosal epithelium, leading to reduced epithelial turnover and renewal, resulting in epithelial breakdown. This results in erythema from increased vascularity and epithelial atrophy 4 to 5 days after the initiation of chemotherapy. At this stage, microtrauma from day-to-day activities such as speech, swallowing, and mastication leads to ulceration. Phase III: Ulcerative/bacteriological phase (pseudomembranous): Epithelial breakdown ultimately results in the ulcerative phase, which occurs within 1 week of therapy. Loss of epithelia and furious exudation lead to the formation of pseudomembranes and ulcers. In this phase, microbial colonization of damaged mucosal surfaces by Gram-negative organisms and yeast occurs, and this may be exacerbated by concomitant neutropenia. Infectious complications arising in neutropenic bone marrow transplantation recipients are among the most challenging aspects of aggressive myelosuppressive antineoplastic drug therapy. There are numerous reports

that demonstrate the importance of ulcerative mucositis as an etiologic factor in the development of systemic a-hemolytic streptococcal infections in the neutropenic cancer patients (11). Phase IV: Healing phase: The duration of this phase usually lasts from 12 to 16 days, and mainly depends on factors such as epithelial proliferation rate, hematopoietic recovery, reestablishment of the local microbial flora, and absence of factors interfering with wound healing viz. infection and mechanical irritation. (12) Clinically the earliest change is characterized by leukoedema. This change presents as a diffuse, poorly defined area of pallor or milky white opalescence most noticeable on the buccal mucosa. Leukoedema will disappear when the mucosa is stretched. Clinical mucositis begins 5-10 days following the initiation of chemotherapy and resolves in 2-3 weeks in more than 90% of patient and correlates with normal white blood cell count. (13) Mucositis manifests as areas of erythema and atrophy on the mucosa that break down to form ulcers which are covered by a yellowish white fibrin clot or pseudomembrane. Peripheral erythema is usually present. Ulcer may range from 0.5cm to greater than 4 cm in maximum dimension. Mucositis pain results in difficulty opening the mouth, dysphagia, and difficulty with oral hygiene. (14) Correct oral hygiene and a good gingival condition during chemotherapy are associated to a lesser incidence and severity of mucositis. (15) Cryotherapy or local utilization of ice chips in the mouth 5 minutes before and during the first 30 minutes of drug infusion has been shown to reduce mucositis with certain chemotherapeutic regimens. (16) Cryotherapy is thought to reduce blood flow to the oral mucosa, minimizing exposure to the toxic effects of chemotherapy. For patients who have difficulty performing oral hygiene or eating because of pain, topical anesthetic agents can be utilized. Examples of topical anesthetics include viscous lidocaine, dyclonine, or diphenhydramine hydrochloride. (17)

Xerostomia (dry mouth)

Saliva serves a number of critical functions in the homeostasis of the oral ecosystem in the oropharynx and larynx, and in speech and swallowing functions. It contains antimicrobial factors that are active against many bacteria and fungi, and buffers the oral pH via bicarbonate and phosphate. (18) Chemotherapy can give rise to a temporary but clinically significant decrease in salivary flow that improves as the bone marrow recovers. (19) The most common medications known to cause xerostomia are diuretics, antihistamines, antipsychotics, beta blockers, and tricyclic antidepressants. Such a decrease in salivary flow in turn favors the appearance of mucositis. (20) 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. 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. (21) Chemotherapy-induced xerostomia is usually of short duration and normal salivary function frequently returns several months after completion of chemotherapy. 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. (22) Other than that patients with xerostomia, whose salivary glands can respond to stimulation may benefit from using simple dietary measures such as eating carrots or celery or by chewing sugarless or xylitol-containing gums. (23)

Dysgeusia

According to some estimates, 50-75% of all cancer patients who receive chemotherapy, radiotherapy or both can experience alterations in taste perception (24). The main cause of dysgeusia in cancer patients is the action of chemotherapy and radiotherapy upon oral epithelial cell turnover, and the effects of such treatments upon nerves, taste buds and olfactory receptors (24). On the other hand, anticancer drugs can access the oral cavity through diffusion from plasma in the capillaries, producing an unpleasant taste (24). The mechanisms underlying dysgeusia also may be related to modifications in the concentrations of sodium, potassium and calcium in the taste bud cell receptors (24). Other causes are candidiasis, viral infections and gingivitis, among others. 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. The evaluation of patients with taste alterations requires a good case history, together with specific questioning (19). We can also deposit solutions with the primary flavors on the back of the tongue, with the purpose of determining whether the patient is able to correctly identify the flavors. Another much less frequently used test is electric stimulation (galvanometry), delivering an electric current of several microamperes onto the back of the tongue, to assess patient capacity to identify the stimulus. 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 (19). 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. Other pharmacological strategies include zinc supplements and amifostine.

Bacterial Infection

During chemotherapy, saprophytic bacteria can become aggressive as a result of the decreased granulocyte presence and increased fragility of the oral mucosa. A number of bacteria, such as *Streptococcus viridans*, *Prevotella*, *Fusobacterium*, *Actinobacillus*, *Actinomycetemcomitans* and *Actinomyces* are associated with infections of the oral cavity in patients receiving chemotherapy (24). Bacterial infections usually manifest locally in the gingival tissue, mucosa and teeth. Necrotizing gingivitis is the most frequent oral manifestation, accompanied in some cases by fever and adenopathies, particularly in patients with previous

periodontal conditions. These infections are usually treated administering a combination of penicillins and metronidazole, with subsequent dental treatment.

Fungal Infection

The majority of fungal infections of the oral cavity are produced by *Candida albicans* (19). The most prevalent forms of candidiasis are the pseudomembranous presentation, followed by erythematous candidiasis and angle cheilitis (19). Oral infection may give rise to sepsis and can prove fatal if not adequately diagnosed, especially when caused by non-*C. albicans* species such as *Candida tropicalis* (22). The diagnosis is based on the clinical appearance of the lesions, the ease with which the necrotic surface of the lesions can be removed by friction, and potassium hydroxide smear preparations, which reveal the presence of the fungus (25). Although prophylactic treatment with antifungal drugs has been questioned, good results have been obtained with such treatment in immune suppressed and/or neutropenic patients (22). In the review of 17 studies published by Lalla et al., the prophylactic administration of fluconazole during cancer therapy was seen to reduce the prevalence of clinically manifest fungal infections, including systemic infections, to 1.9% (22). Topical and systemic antifungal treatment is used for oral candidiasis, combining nystatin (100,000 IU/ml 3-4 times/day) and fluconazole (100 mg/day) or ketoconazole (200 mg/day). In the case of resistance to these drugs, use is made of itraconazole (200-400 mg/day) or amphotericin B, in patients with very extensive and severe infections (20 mg/day) (22)

Dental caries

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 hyposalivation (26). In adults, a number of studies have reported an increase in caries in patients subjected to chemotherapy (27)

Viral Infection

In most cases, viral infections produced by herpes simplex virus, varicella zoster virus and Epstein-Barr virus are the result of reactivation of a latent virus, while infections produced by cytomegalovirus can be due to reactivation of a latent virus or the action of a recently acquired virus (19). Infection produced by herpes simplex virus (HSV). The incidence of oral lesions produced by recurrent HSV in cancer patients with bone marrow suppression has decreased considerably following the introduction of prophylactic acyclovir (19). In patients without antiviral prophylaxis, the oral lesions generally manifest with chemotherapy or chemotherapy-radiotherapy during the most intense immune suppression period. The clinical picture tends to be atypical, with painful ulcerations as a first manifestation. These lesions are crater-shaped, well defined with whitish margins, and are mainly located on the palate and gums (28). The ulcers tend to progress towards mucocutaneous lesions in a short period of time, and are slow in healing. The diagnosis is usually based on the clinical findings, though in some cases viral culture and isolation is recommended in order to confirm the diagnosis and avoid spreading of the lesions (28). Treatment consists of acyclovir via the oral (200-400 mg/3-5 times a day) or intravenous route (5 mg/kg in infusion during one hour every 8-12 hours), for as long as lesions remain (29).

Hemorrhage

Chemotherapeutic agents may secondarily induce thrombocytopenia, which is the most common cause of intraoral bleeding. Hemorrhage may occur anywhere in the mouth and may be spontaneous, traumatically induced, or result from existing disease. Hemorrhage may present clinically as gingival bleeding or submucosal bleeding with hematoma formation. Profound thrombocytopenia (<20,000 mm³) is responsible for these changes, however qualitative platelet characteristics are also altered during chemotherapy. (30) When the hemopoietic tissues are suppressed by chemotherapeutic regimens and reach their nadir, maximum stomatotoxicity occurs. Recovery of the oral mucosa precedes recovery of the bone marrow by about 2 to 3 days and ultimately predicts the recovery of the hemopoietic tissues. (31) Bleeding potential can be assessed by laboratory testing. The thrombocyte count gives the provider the quantity of platelets and the bleeding time will show the quality and function of the platelets. Prevention is the key to controlling hemorrhage. This is accomplished before chemotherapy begins by eliminating potential areas of trauma such as sharp restorations, fractured teeth, orthodontic brackets, or any other pre-existing oral disease. When platelet counts are below 20,000 mm³, conventional oral hygiene may be too traumatic. (32) In these cases, the modified mechanical approach discussed earlier should be implemented. Accumulated blood should be removed in order to identify the bleeding site and then pressure should be applied with moist gauze, periodontal packing, or a mucosal guard. A variety of topical antihemorrhagic agents may be used, such as absorbable gelatin sponges, oxidized cellulose, aminocaproic acid, thrombin, or tranexamic acid. If necessary, dental treatment may be accomplished at this time if platelet counts are greater than 50,000 mm³. However, if platelet counts fall below this level, the benefit of dental care may not outweigh the risk. If the hemorrhage is the result of an infection and surgical intervention is necessary, a platelet transfusion should be accomplished prior to the surgery. (33)

Osteoradionecrosis

Osteoradionecrosis of the jaws is a delayed injury caused by the failure of bone healing following chemotherapy for head and neck cancer. (34) It may occur in approximately 5% of patients. Osteoradionecrosis most commonly affects the mandible and is

staged according to the treatment indicated¹⁵⁵ or by lesion size and symptoms. (35) Lesions surrounded by attached or keratinized tissue appear to have a better prognosis, while those involving cortical bone may progress to pathologic fracture and oral-extraoral or oral-antral fistula. Severe osteoradionecrosis is debilitating and can compromise quality of life and functional prognosis. Risk factors for osteoradionecrosis include chemotherapy, oral surgery, time elapsed between extractions and chemotherapy, presence and progression of dental and periodontal disease, association of the tumor with bone, and the high-dose volume of the horizontal ramus of the irradiated mandible. (36) Comorbidities that may increase the risk of osteoradionecrosis include diabetes and collagen vascular disease, tobacco or alcohol abuse, and poor nutrition. The primary approach to the management of osteoradionecrosis is prevention with comprehensive dental evaluation and treatment prior to chemotherapy. Managing osteoradionecrosis involves managing the comorbid factors; optimizing oral hygiene, controlling infection with the use of chlorhexidine rinses and systemic antibiotics; nutritional support; devitalized tissue removal (sequestrectomy) and symptom management; and reduction of dental extractions through preventive dental management, endodontics, and crown amputation.⁽³⁵⁾

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