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**REVIEW ARTICLE**

# ORAL COMPLICATIONS IN PATIENTS UNDERGOING CHEMOTHERAPY

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**ABSTRACT**

Cancer is a disease characterized by out of control cell growth. It is also the common term for neoplasm, or tumors that are malignant. All cancers are caused by the malfunction of genes that control cell growth, division and maturation, which later progresses to abnormal or uncontrolled cell division. Chemotherapy is responsible for the long term survival of patient with malignancies. Chemotherapeutic treatment has deleterious effect on both normal cells and tumor cells provided that certain normal cells of oral mucosa which divide rapidly are also affected. Thus, the effect of chemotherapy may result in oral complications such as mucositis, xerostomia, osteoradionecrosis etc. These complications have a negative impact upon patients' quality of life and could be life threatening in serious cases.



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## INTRODUCTION

Cancer is also known as a malignant tumor or neoplasm. It 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 is 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 while internal factors include inherited mutations, hormones, immune conditions, and mutations occurring from errors in metabolism. All of these factors may initiate the process of carcinogenesis. Chemotherapy is the most widely used treatment for cancer. The great inconvenience of chemotherapy is its lack of selectivity, since it acts upon both tumor cells and rapidly multiplying normal cells (Ilgenli *et al*., 2001). Although the objective of treatment employed is to improve the patient's quality of life, they are associated with several side effects. Up to 40% of all patients undergoing cancer chemotherapy develop acute oral complications (Caribé-Gomes, 2002). Oral complications that arise with chemotherapy include mucositis, xerostomia, bacterial, fungal, dental caries, dysgeusia and osteoradionecrosis (Naidu *et al*., 2004).

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The oral cavity is very susceptible to the direct and indirect toxic effects of chemotherapy 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 (Franzén *et al*., 1992). It is therefore essential to evaluate the oral condition of the patient and to stabilize any oral disease conditions before cancer treatment is provided (Sonis, 1998).

### Oral Complications in Patients Undergoing Cancer Chemotherapy

### Mucositis

Mucositis is a complication in patients receiving chemotherapy, bone marrow transplantation and local irradiation for tumors in the head and neck area (Treister, 2007). The probability of developing mucositis depends upon the treatment. It is estimated that about 40% of patients treated with standard chemotherapy develop mucositis (Treister, 2007). The mucosal injury increases with the increasing number ofchemotherapy cycles. The degree and duration of mucositis in patients treated with chemotherapy are related to radiation source, cumulative dose, intensity, volume of radiated mucosa, smoking, alcohol consumption, and oral hygiene (Ruescher *et al*., 1998). 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 (Sonis, 1998).

Mucositis develops in 4 phases: initiation, message generation, signal amplification, ulceration, and healing phase. Phase I: Initial inflammatory or vascular phase. During this phase, exposed cells in the buccal mucosa release free radicals, modified proteins, and proinflammatory cytokines, prostaglandins, and tumor necrosis factor (TNF). These are inflammatory mediators, which can cause further damage either directly or indirectly by increasing vascular permeability, thereby enhancing cytotoxic drug uptake (Toscano *et al*.,). Phase II: Epithelial phase: In this phase, chemotherapy radiation retards cell division in the oral mucosal epithelium, leading to reduced epithelial turnover and renewal resulting in epithelial breakdown. At this stage, microtrauma from activities such as speech, swallowing and mastication leads to ulceration. Phase III: Ulcerative/bacteriological phase (pseudomembraneous): 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 and yeast occurs then exacerbated by concomitant neutropenia. Neutropenic bone marrow transplantation recipients have infectious complications arising in neutropenic bone marrow and these are among the most challenging aspects of aggressive myelosuppressive antineoplastic drug therapy. Number of cases report that demonstrate the importance of ulcerative mucositis as an etiologic factor in the development of systemic a- hemolytic streptococcal infections in the neutropinic cancer patients (Epstein, 2003). Phase IV: Healing phase: This phase lasts usually from 12 to 16 days and mainly depends on factors such as epithelialproliferation rate, hematopoietic recovery and reestablishment of the local microbial flora (López, 2014).

Clinically the earliest change is characterized by leukoedema. Leukoedema will disappear when the mucosa is stretched. Clinical mucositis begins 5-10 days following the initiation of chemotheraphy and resolves in 2-3 weeks in more than 90% of patient and correlates with normal white blood cell count (Cascinu *et al*., 1994). Mucositis pain results in difficulty opening the mouth, dysphagia, and difficulty with maintaining good oral hygiene (Wilkins, 1989). Good oral hygiene and a gingival health during chemotherapy are associated to a lesser incidence and severity of mucositis (Epstein, 1992). 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 (López *et al*., 2011). 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 (Ruiz-Esquide *et al*., 2011).

**Xerostomia (dry mouth)**

Saliva serves a number of critical functions oral ecosystem in the oropharynx and larynx, aiding 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 (Chan, 2003). Chemotherapy treatment for cancer can give rise to a temporary side effects but clinically significant decrease in salivary secretion (Mosel *et al*., 2011). The most common medications known to cause xerostomia are diuretics, antihistamines, antipsychotics, beta blockers, and tricyclic antidepressants. This decrease in salivary flow in turn favors the appearance of mucositis (Wilkes, 1998). The symptoms of xerostomia includeburning sensation, cracked lips, changes in the tongue surface, and problems in wearing removable dentures or drinking. 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 (Cowart, 2011). In treating xerostomia it is advisable to maintain adequate oral hydration by means of regular intake of water, the use of saliva substitutes or cholinergic agonists such as pilocarpine, cevimeline or bethanechol (Caribé-Gomes, 2003).

**Bacterial Infection**

Saprophytic bacteria can become aggressive as a result of the decreased granulocyte presence and increased fragility of the oral mucosa affected by chemotherapy. A number of bacteria, such as Streptococcus viridans, Prevotella, Fusobacterium, Actinomycetemcomitans and Actinomyces are associated with infections of the oral cavity in patients receiving chemotherapy (Galindo *et al*., 2006). Bacterial infections manifest locally in the gingival tissue, mucosa and on teeth surface. Oral cavity commonly necroses, particularly resulting in patients developing periodontal conditions. These infections are usually treated by administering a combination of and metronidazole, with subsequent dental treatment and follow up appointments.

**Dental caries**

Some authors have described an increased incidence of caries in oral cavity can also be subjected to chemotherapy, though the data are controversial, due to caries may result from an increased use high sugar content of rinses to treat hyposalivation (Glenny). In adults, a number of studies have reported an increase in caries in patients subjected to chemotherapy (Naylor, 1988).

**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 previously existing disease. It may present clinically as gingival bleeding, submucosal bleeding with hematoma formation. Profound thrombocytopenia (<20,000 mm3) is responsible for these changes, however qualitative platelet characteristics are also altered during chemotherapy (Caprini, 1982). 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 (Blanchard, 2011). 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. When platelet counts are below 20,000 mm3, conventional oral hygiene may be too traumatic (Epstein *et al*., 1987). 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, 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 (Glanzmann, 1995).

**Viral Infection**

Viral infections produced by herpes simplex virus, varicella zoster virus and Epstein-Barr virus are the result of reactivation of a latent virus, while the infection spreads produced bycytomegalovirus can be also due to reactivation of a latent virus or the action of a recently acquired virus (Chan *et al*., 2003). 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 (Chan *et al*., 2003). In patients without antiviral prophylaxis, the oral lesions generally manifest with chemotherapy during the most intense immune suppressing period.

These lesions are crater- shaped, well defined with whitish margins, and are mainly located on the palate and gums (Chan *et al*., 2003). The ulcers tend to progress towards lesions in a short period of time and provide slow healing. The diagnosis is based on the clinical findings but in some cases viral culture and isolation is recommended in order to confirm the diagnosis and avoid further spreading of the lesions (Chan *et al*., 2003). Treatment consists of acyclovir via the oral or intravenous routes, for as long as lesions remain (Heimadahl, 1999).

**Fungal Infection**

The majority of fungal infections of the oral cavity are produced by microbe Candida albicans (Chan *et al*., 2003). The most prevalent forms of candidiasis are the pseudomembranous presentation, followed by erythematous candidiasis and angle cheilitis (Chan *et al*., 2003). Oral infection may give rise to sepsis and can prove fatal if not adequately diagnosed. 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 to indicate the presence of the fungus (Sepúlveda *et al*.).

Although prophylactic treatment with antifungal drugs has been questioned, good results have been obtained with such treatment in immunosuppressed patients (Cowart, 2011). 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 (Caribé-Gomes, 2003).

**Osteoradionecrosis**

Osteoradionecrosis of the jaws is a delayed injury caused by the failure of bone healing following chemotheraphy for head and neck regions cancer (Marx, 1983). Osteoradionecrosis most commonly affects the mandible and is staged according to the treatment indicated or by lesion size and symptoms showing (Marx, 1983). Severe osteoradionecrosis can compromise quality of life and prognosis. Risk factors for osteoradionecrosis include oral surgery, time elapsed between extractions and chemotheraphy, 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 (Beumer, 1984). Comorbidities that may increase the risk of osteoradionecrosis include diabetes and collagen vascular disease and poor nutrition.

Managing osteoradionecrosis involves managing the comorbid factors which are optimizing oral hygiene, controlling infection with the use of chlorrhexidine rinses and systemic antibiotics, nutritional support, devitalized tissue removal and reduction of dental extractions through preventive dental management and crown amputation (Wong *et al*., 1997).

**Oral candidiasis**

Candida albicans is the most opportunistic pathogen to reside in oral cavity. The fungal infection weaken the host or causing immunocompromised (Jackson, 2007; Wu *et al*., 2003; Achkar, 2010). The pathogen spreading can either be superficial or deep in the tissue attacking bloodstream internal organs (López-Martínez, 2010).

The candida species can associate with the virulence attributes and also host factors (Samaranayake *et al*., 1986). Further infection may spread and cause oropharyngeal candidiasis resulting in acute pseudomembranous thrush, angular cheleitis and acute atrophic (Farah *et al*., 2000).

**Taste alteration**

Some authors include taste alteration induced by chemotherapy. Taste alteration is common in chemotherapy and often produces negative impact to food selection, the quality of life and nutrition (Mizukami *et al*., 2016). Taste disorders are unpleasant experiences, it alters the taste signals of regular meal and affects the food intake. It plays an important role for causing anorexia, loss of weight and malnutrition (Payakachat *et al*., 2013).

**Conclusion**

Radiotherapy-induced damage in the oral mucosa is the result of the deleterious effects of chemotherapy radiation, not only on the oral mucosa itself but also on the adjacent salivary glands and oral innervation. The complications such as mucositis, xerostomia, dental caries, infections and candidiasis as well as taste alteration are complex and some with dynamic pathological process which have negative impacts on quality of life and nutrition.

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