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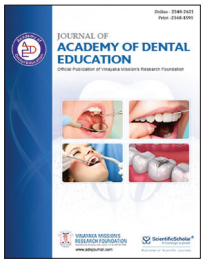

Review Article

Effects of chemotherapy on oral mucosa

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ABSTRACT

Cancer leads to several oral and dental complications arise during the course of a malignant condition, oral or non-oral. These are largely due to the direct effect of cancer but may also result from the complication of treatment modality undertaken to cure the malignancy. This article elaborates on complications of the chemotherapeutic agents, which when employed to combat cancerous cells, may target the host cells. The oral complications of such a therapy results in several conditions like oral mucositis, infections, hemorrhage, salivary alterations, dysgeusia, lichenoid reactions amongst others. Thus, an in-depth understanding of these complications is a must in order to provide better care for an already frail and ailing patient.

Keywords: Chemotherapy, Cancer, Oral mucosa, Dental considerations, Chemotherapeutic agents, Mucositis

INTRODUCTION

Several oral and dental complications arise during the course of a malignant condition, oral or non-oral. Most of these are due to the direct effect of cancer but many may be a result of the complication of treatment modality undertaken to cure the malignancy. These complications further result in a poor quality of life, substantial comorbidities, change in course of effective treatment plans and dosage, nutritional delays, etc. An ideal chemotherapeutic drug should be able to differentiate between healthy tissues and malignant cells. Unfortunately, this is not a feature of drugs available yet. Therefore, this inevitable damage to healthy cells is an acceptable but challenging outcome. Cells undergoing rapid replication such as skin, mucous membranes, hair, and hematopoietic system take the brunt of this.

ETIOPATHOGENESIS

The anti-cancer medication acts on various tissues either directly or indirectly. The side effects due to direct action of such drugs begin with the tissues of the oral cavity. It occurs by virtue of their indiscriminate impact on the cell replication cycle. Oral mucous membrane under the influence of these cytotoxic agents faces destruction of the proliferating basal cell layer. Cell turnover of the superficial layers of the mucous membrane is adversely affected causing ulceration (1). The side effects were seen indirectly due to damage and suppression of bone marrow, immune cells, and secretory protective agents.[1]

CHEMOTHERAPEUTIC AGENTS USED

The kind antineoplastic drugs used are an important consideration but so are the dosage and frequency of its delivery. Oral mucosa is most prominently affected by drugs such as vinca alkaloids

such as vinblastine and vincristine; alkylating drugs such as cyclophosphamide, busulfan, and procarbazine; antimetabolites such as methotrexate, fluorouracil, cytosine arabinoside, hydroxyurea, mercaptopurine, and thioguanine; anthracyclines such as doxorubicin and daunorubicin; and antibiotics such as actinomycin D, mitomycin, and bleomycin.[2] DNA replication and mucosal cellular proliferation are inhibited further reducing the cell turnover of the basal layer leading to stomatotoxicity. This includes mucosal atrophy, breakdown of collagen, bleeding, and ulceration. Further, thrombocytopenia and leukopenia occur causing hematopoietic and immune disturbances. Bone loss, bleeding, and pulpal conditions ensue causing various dental issues.[3]

EFFECTS OF CHEMOTHERAPEUTIC AGENTS

Oral mucositis

It is a painful inflammatory condition of the oral mucous membrane. Characteristically, the infiltration of the inflammatory cells is observed along with tissue disruption and ulceration. It occurs within 4–7 days of initiation of a high-dose chemoregimen. It lasts up to 2–4 weeks post-completion of the treatment. It is most significantly associated with methotrexate, doxorubicin, bleomycin, and fluorouracil.[4] Its first sign is erythema, followed by a burning sensation, edema, deep-seated pain, and ulceration which impair speech, mastication, deglutition, etc. Administration of opioids such as morphine and dietary changes is helpful in such a stage. They are ill-defined ulcers, covered by a pseudomembranous layer, and heal without scar formation. They are observed mostly on the buccal and labial mucosa, the floor of the mouth, the lateral border of the tongue, and soft palate. Risk factors involving patients' age, deficiency diseases, pre-existing medical issues, poor oral health, trauma, liver, and kidney disease increase the risk of developing mucositis. Excessive presence of *Porphyromonas gingivalis* has also been shown to aggravate ulceration and mucositis.[5] High dose and frequency of the drug and administration of drugs that act on DNA such as methotrexate and fluorouracil have been shown to increase the chances of developing oral mucositis.[6]

Hemorrhage

It occurs secondarily to bone marrow suppression and hepatotoxicity due action of cytostatic drugs such as methotrexate, doxorubicin, vinblastine, etoposide, and fluorouracil, suppressing formation of coagulation factors in the blood. Bleeding can be appreciated in patients during mastication, especially in patients with a history of gingivitis and periodontal disease. Clinically, the oral cavity presents with petechial spots, ecchymosis, hematomas, or diffuse hemorrhage at any location. Caution is needed to not disturb the blood clots since this might cause additional hemorrhage (4). Mouth rinse with 0.12% chlorhexidine can be used to avoid superimposed infection. Emergency treatment in such patients necessitates the use of vasoconstrictors like adrenaline, cyanoacrylate much adherent tissue protectors, hemostatic collagen, topical thrombin, etc. In case of invasive dental treatment, platelet count should be at least 50,000/mm3, the procedure should be carried out within the hospital setting, following transfusion assessment with opinion from the primary oncologist.[7]

Xerostomia and salivary alterations

Chemotherapy produces a short term and clinically relevant decrease in salivary secretion which gradually improves with the recovery of bone marrow.[7] The symptoms of mucositis and xerostomia or dryness include dryness, burning sensation or discomfort, atrophic tongue, and cracked lips. Dysgeusia and pain occur secondary to the consequences of therapy on the papillae of the tongue, causing demyelination of the nerve fibers.[8] Care should be taken to increase the intake of water, the utilization of salivary substitutes if required or cholinergic agonists which together favor the maintenance integrity of the oral mucous membrane.[9] Chemotherapeutic agents have an adverse effect on the salivary elements such as immunoglobulins and enzymes such as peroxidases and amylases. Immunoglobulins present in the saliva shield the mucous membrane against possible insults and infections. A decrease in their secretion may cause issues with the chemotherapy.[10] A change in the buffer capacity of saliva is also noticed following the administration of cytostatic agents.[11]

Dysgeusia

About 50–75% of all cancer patients who receive chemotherapy are shown to experience alterations in gustatory sensation.[12] The oral somatic cell turnover is reduced during chemotherapy and affects the nerves, taste buds, and exteroception receptors.[10] The medicines themselves would also produce as bad taste in the mouth. Mycosis, infections, and periodontal disease may also cause it. The patients describe the less or dreadfully salty taste. Such a side effect would also lead to reduced food intake. Reducing the medication dose, the treatment of oral infections, and proper diet,[12] increased liquid intake with meals, chewing food slowly, and diversifying flavor throughout meals are some steps that can be taken to forestall tongue adaptation to flavors. Inclusion of Vitamin D, Zn supplements, and amifostine can also help and is under investigation.[12]

Infections

The oral mucous membrane reduces levels of oral microorganisms colonizing the mucosa by shedding the surface

layer; it additionally limits penetration of the many compounds into the epithelial tissue by maintaining a chemical barrier.

Bacterial infections

Periapical lesions left untreated might reach osteitis of the jaws. Pain, suppuration, and even fistulae are common which require treatment with broad-spectrum antibiotics. Rarely, sinus occlusion and Ludwig angina may also occur due to progressive infection, requiring aggressive medical care.[13] Sialadenitis can occur producing severe pain and swelling. Parotid sialadenitis is usually caused by *Staphylococcus aureus*.[14] Necrotizing ulcerative gingivitis and periodontal disease could be a common finding in patients requiring chemotherapy. Pericoronitis usually arises within the space of the third molars showing ulceration, mortification, and severe pain. Treatment includes prophylaxis, extraction of the tooth, and antibiotics such as penicillin, clindamycin, or metronidazole.[15] The dental and periodontal problems must be treated and teeth with unfavorable prognosis should be extracted before chemotherapy to reduce the incidence of oral complications associated with the chemotherapeutic procedure at least 10 days before the initiation of chemotherapy.[7]

Fungal

Candidiasis is often caused by opportunist overgrowth of *C. albicans*. The use of antibiotics might alter the oral flora along with drug- or disease-induced immunosuppression, injury, and reduced salivary flow together providing a positive setting for candidiasis.[16] The mean prevalence of oral mycosis throughout chemotherapy is 38%.[17] Most commonly it includes pseudomembranous and erythroderma candidiasis.[18] Topical antifungal rinses used with variable effectivity in preventing or treating mycosis in neutropenic patients.[19] Systemic fluconazole is an effective drug for prophylaxis and treatment in such patients.[17] Non-candidal fungal organisms are increasingly been associated with immunocompromised cancer patients such as *Aspergillus*, *Mucormycosis*, and *Rhizopus*.[19] This demands prompt medical care due to the high risk of morbidity and mortality.

Viral

HSV is quite prevalent in immunosuppression due to chemotherapy. Neutropenic patients are at the utmost risk during treatment.[20] Acyclovir and valacyclovir are efficacious in the prevention and treatment of HSV.[21] Oral hairy leukoplakia due to Epstein-Barr virus infection manifests in patients under cancer treatment even if they are HIV negative. It is most commonly seen in chemo or corticosteroid regimen patients, undergoing therapy for acute myelogenous leukemia, acute lymphocytic leukemia, and multiple myeloma. High-dose valacyclovir can be administered safely and effectively as a drug of choice.[22]

Dental changes

Chemotherapy causes esthetic and clinical dental issues, principally in children undergoing treatment at <5 years of age. The shape and size of the primary crown do not seem to be affected since the morphology is decided before birth. It causes macrodontia, morphological anomalies of the dental roots of canines, premolars, and molars.[9] Hypoplasia, discolorations, and opacifications in the enamel also occur due to the side effects of chemo agents on odontogenesis.[23] In adults, a variety of studies have reported a rise in decay in patients subjected to therapy.[8]

Neurological issues

Vinca alkaloids, vincristine, and vinblastine cause direct neurotoxicity. Deep pain and acute pulpal disease are quite common and require a thorough history and oral physical examination to be performed, along with radiographs and vitality testing of the dental pulp. Treatment modalities include pain support and counseling. The symptoms resolve post a week of discontinuing the chemotherapy. Dental hypersensitivity after discontinuation of therapy is seen within weeks or months. Temporomandibular joint pain involving muscles of mastication may ensue.[24]

Osteonecrosis

Osteonecrosis impairs osteoclasts and osteoblasts that are closely involved with bone health and repair. Osteonecrosis is often caused by injury, extraction, biopsy, pathology, malignancy, or even some drugs. Edema, erythema, ulceration, paresthesia, and mobility of tooth are also observed.[25] Bisphosphonates are principally accountable for osteonecrosis of the jaws. They are used against bone metastases, osteoporosis, and skin cancer.[7] ONJ is intense in patients receiving sunitinib and bisphosphonates. Sunitinib causes mucositis and this destruction of epithelial tissue could be vital for the development of ONJ. A clinical finding of exposed bone in the mouth for 8 weeks or longer, despite good medical intervention, is a distinctive diagnostic feature of ONJ.[26]

Lichenoid reactions

A lichenoid reaction shows characteristic lesions of whitish lace-like papules, erythematous erosions, and plaques with divergent radiating striae. It disappears, either straightaway when the agent's action is completed, or will persist. In addition, microscopic anatomy examination reveals leukocyte infiltration, distinguished parakeratosis, acanthosis, vascular inflammation, etc., that are not seen in oral lichen planus.

Imatinib mesylate is the drug of choice against chronic myeloid leukemia. It's to blame for lichenoid lesions of the oral mucous membrane, skin, or nails. Lichenoid reaction lesions could be due to altered expression of dermal markers due to the imatinib. The management of LRs needs the termination of the precipitating agent or the use of corticosteroids.[27]

Melanosis

Imatinib has been shown to cause hyperpigmentation. It is evidenced to be dose connected and reversible once administration ceases. Imatinib causes excessive melanogenesis in certain epidermal and membranous areas. It seems that imatinib binds to receptors within the skin activating or inhibiting melanogenesis. Reports have delineated bluish-brown pigmentation on the surface.[28]

Nutritional effects

Patients with head-and-neck cancer are at high risk for dietary problems. It may be due to the malignancy itself, poor nutrition or complications of surgery or chemotherapy, loss of appetite secondary to mucositis, xerostomia, taste loss, dysphagia, nausea, or vomiting. Quality of life is compromised as ingestion becomes problematic. Oral pain with ingestion might result in the choice of foods that do not worsen the pain or discomfort at the expense of adequate nutrition. Dietary deficiencies can be managed by seeking dietary counseling, changing the feel and consistency of food, and by having frequent meals and snacks.[29]

General side effects

The bone marrow suppression leads to leukemia observable in peripheral blood toward day 10 from the start of chemotherapy. Thrombocytopenia can be seen after 10–14 days and later on, anemia. Nausea, vomiting, alopecia, hand-foot syndrome, and paresthesias will also begin developing. Most of these disappear soon after the end of chemotherapy although in some cases permanent harm could also be ascertained such as myocardiopathy, pulmonary fibrosis, chronic renal failure, or sterility.[7]

CONCLUSION

Modern cancer treatment includes surgery, chemotherapy, radiotherapy, and immunotherapy either alone or in combination. Chemotherapy leads to insult to oral structures directly and their systemic toxicity causes indirect symptoms. The oral complications may occur throughout and after cancer treatment. It includes mucositis, dysgeusia, and infectious diseases. Poorly restorations, periodontal disease, and other pathologies associated with poor oral hygiene and sequelae of aggressive cancer treatment can affect patients' quality of life tremendously. It is, therefore, important that optimal oral health care must be maintained. It is of utmost importance for everyday functions such as eating and verbal and non-verbal communications.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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