

Oral Complications of Non-Surgical Cancer Therapies: A Review

Abstract

Aggressive treatment of malignant disease may produce unavoidable toxicities to normal cells. The oral cavity is highly susceptible to direct and indirect toxic effects of cancer chemotherapy, ionizing radiation and Hematopoietic Stem Cell Transplantation. These complications may include mucositis, xerostomia, dental caries, loss of taste, trismus, infection, osteoradionecrosis, and abnormalities of growth and development. It is essential that a multidisciplinary approach be used for oral management of the cancer patient before, during, and after cancer treatment. Preventing and treating oral complications of cancer therapy involve identifying the Patient at risk, starting preventive measures before cancer therapy begins, and treating complications as soon as they appear. These patients can visit a dentist for management of their complications. So, as a dentist we need to be well aware of the possible complications and their management.

Key Words

Chemotherapy; oral mucositis, Radiotherapy, Xerostomia

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INTRODUCTION

Aggressive treatment of malignant disease may produce unavoidable toxicities to normal cells. The oral cavity is highly susceptible to direct and indirect toxic effects of cancer chemotherapy, ionizing radiation and Hematopoietic Stem Cell Transplantation (HSCT). These complications may include mucositis, xerostomia, dental caries, loss of taste, trismus, infection, osteoradionecrosis, and abnormalities of growth and development. It is essential that a multidisciplinary approach be used for oral management of the cancer patient before, during, and after cancer treatment. Preventing and treating oral complications of cancer therapy involve identifying the Patient at risk, starting preventive measures before cancer therapy begins, and treating complications as soon as they appear. These patients can visit a dentist for management of their complications. So, as a dentist we need to be well aware of the possible complications and their management.

ORAL TOXICITY IN CHEMOTHERAPY PATIENTS

Oral Mucositis

Mucositis is an acute injury to the mucosal lining of the head and neck region associated with cancer

treatment. Chemotherapy-induced stomatitis is typically less severe and of shorter duration (3-12 days). The use of concurrent chemotherapy with RT shortens the onset, exacerbates the severity, and prolongs the duration of mucositis. The clinical recognition of mucosal changes range from mild erythema to deep mucosal ulceration. The ulcers are typically covered by exudates composed of cells, serum, and debris, so this more advanced stage is interchangeably referred to as "ulcerative," "fibrinous" or "pseudomembranous" mucositis.¹

Management of Mucositis:

There is no current Food and Drug Administration (FDA) - approved intervention for the prevention of Oral Mucositis. Current therapy consists of symptom management.

Prophylactic measures and treatment options should be employed by practitioners for patients in the appropriate clinical settings. Specific recommendations for minimizing oral mucositis include the following:

1. Good oral hygiene.
2. Avoidance of spicy, acidic, hard, and hot foods and beverages.
3. Use of mild-flavored toothpastes.
4. Bland rinses:



Fig. 1: Pseudomembranous Candidiasis



Fig. 2: Radiation Caries



Fig. 3: Hypodontia, microdontia inverted & impacted premolars & stunted permanent teeth root



Fig. 4: Osteoradionecrosis

- Saline mouthwash (1 teaspoon of salt mixed with 500ml of lukewarm water)
- Sodium bicarbonate mouthwash (2 teaspoons of sodium bicarbonate in 500ml of lukewarm water)
- Saline & sodium bicarbonate mouthwash. (In 1 cup (250mls) of lukewarm water dissolve - ¼ teaspoon of bicarbonate + ¼ teaspoon of salt)
- 5. Topical anesthetics:
 - Lidocaine: viscous, ointments, sprays.
 - XYLOCAINE spray (Indian Pharmacopoeia)
 - Benzocaine: sprays, gels.
 - MUCOPAIN gel (Indian Pharmacopoeia)
- 6. Dyclonine HCl lozenges (US Pharmacopoeia): 1 lozenge (1.2, 2 or 3mg) repeat after 2 hours if necessary.
- 7. Diphenhydramine HCl : Benadryl syrup (Indian Pharmacopoeia).
- 8. Analgesics: Benzylamine HCl topical rinse (not approved in the United States). TANTUM Oral Rinse- 15mL 1-3hourly for not >7days (Indian Pharmacopoeia).
- 9. Opioid drugs: Oral, intravenous (e.g., bolus, continuous infusion, patient-controlled analgesia), patches, transmucosal.
- 10. Growth factor (keratinocyte growth factor-1): Palifermin (approved by the FDA in December 2004 to decrease the incidence and duration of severe oral mucositis in patients undergoing high-dose chemotherapy with or without

radiation therapy followed by bone marrow transplant for hematologic cancers).^[2]

KEPIVANCE 60 mcg/kg/day, administered as an intravenous bolus injection for 3 consecutive days before and 3 consecutive days after myelotoxic therapy, for a total of 6 doses (US Pharmacopoeia). Updated guidelines from the American Society of Clinical Oncology for the prevention and treatment of mucositis were published in 2007¹ and include the following:

- Palifermin for oral mucositis associated with stem cell transplantation.
 - Amifostine for radiation proctitis.
- CYTOFOS vial - 200mg/m² BSA once daily infusion given over 3mins, 15-30mins before radiotherapy (Indian Pharmacopoeia)
- Cryotherapy for high-dose-melphalan-induced mucositis.

Oral Pain

Oral Pain is commonly seen in cancer patients undergoing chemotherapy. Most patients require both systemic and topical analgesics. Narcotic dose, frequency, and duration should be regularly adjusted to meet the intensity level of pain. Pain management by patient-controlled analgesia with morphine in HSCT or transdermal fentanyl in conventional and high-dose chemotherapy with or without total body irradiation, 2% morphine mouthwash in head & neck radiation therapy, or 0.5% doxepin mouthwash have been recommended

or suggested depending on the level of evidence as interventions to treat pain due to oral mucositis. Transdermal fentanyl (DUROGESIC) is useful in HN patients who often have a limited ability to swallow solids.

Oral Hemorrhage

Compromised basic oral care increases the risk of oral infection (gingivitis, periodontitis, oral candidiasis), which increase the risk of oral hemorrhage. The bleeding can be spontaneous, traumatically induced, or effect from existing pathology.^[3] In patients receiving high-dose chemotherapy, hemorrhage may also be caused by cancer treatment-induced thrombocytopenia. Management of Oral hemorrhage in these cases will be by treating the underlying gingivitis or periodontitis with scaling and antibiotics therapy.

Dysgeusia

Chemotherapeutic agents such as cyclophosphamide, dacarbazine, doxorubicin, 5-FU, methotrexate, nitrogen mustard, cisplatin, and vincristine frequently damage our taste buds causing taste alterations (Camp-Sorrell, 2005). Patients may experience a metallic or "chemical" taste when chemotherapy is delivered, and this is consistent with drug secretion in saliva (Epstein & Barasch, 2010). Currently, no guidelines exist for the pharmacologic management of dysgeusia. Non-pharmacologic management strategies and patient education has been the mainstay. Several published studies along with The American Institute for Cancer Research (2010) suggest the following for improving the flavor of foods:

- Consume foods that are cold or at room temperature.
- Avoid the use of metallic silverware.
- Add more seasonings and spices to foods, such as salt, oregano, basil, cinnamon, and ginger.
- Add sugar to decrease salty or bitter tastes.
- Choose frozen fruits such as melon balls, grapes, or oranges.
- Choose more bland foods.
- Suck on hard, sugarless candies.
- Drink more water with meals to help with swallowing or rinse away bad taste.
- Eat small meals several times a day.

In addition to modifying food preparation techniques, cognizant oral mouth care, frequent oral hygiene such as regularly rinsing the mouth and brushing the teeth can be advised.

Oral Infections

Chemotherapy-related oral infections, which account for 25-50% of the total infections, contribute significantly to the morbidity and mortality in these patients. Susceptible areas include teeth, gingiva, salivary glands, and mucosa. It should be noted that in the myelosuppressed patient the cardinal signs of infection such as erythema and swelling are not always present. Therefore, the more reliable indicators such as fever, pain, and the appearance of lesions should be used to closely monitor all suspected infections.^[4] Common oral flora and opportunistic microorganisms include coagulase negative Staphylococci and Streptococci, Klebsiella Pneumonia, Pseudomonas Aeruginosa and Escherichia coli. It has been shown that pathogenic microorganisms found subgingivally or in periradicular area may cause acute exacerbations of preexisting periodontal or periradicular infections when the granulocyte count dips below 1000/mm.^[3,5] The most dangerous complication in the realm of infections comes from fungal species, most notably Candida species. The mortality rate from systemic fungal infections is much higher compared to other infections, with the majority believed to have originated from the oral cavity.

Viral infections frequently seen in patients undergoing chemotherapy include the herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV).

ORAL TOXICITY IN HEAD & NECK RADIATION PATIENTS

Head and neck radiation can cause a wide spectrum of oral complications.

Acute/ Immediate complications:

- a. Oral mucositis.
 - b. Infection: Fungal, bacterial.
 - c. Salivary gland dysfunction: Sialadenitis, xerostomia.
 - d. Taste dysfunction.
- Long term/ Chronic complications:
- a. Mucosal fibrosis and atrophy.
 - b. Xerostomia.
 - c. Dental caries.
 - d. Soft tissue necrosis.
 - e. Osteonecrosis.
 - f. Taste dysfunction: Dysgeusia, ageusia.
 - g. Muscular/cutaneous fibrosis.
 - h. Infections: Fungal, Bacterial.

Unlike chemotherapy, however, radiation damage is anatomically site-specific. Degree of damage depends on treatment regimen-related factors,

including type of radiation utilized, total dose administered, and field size/fractionation.

Radiation Mucositis

Radiotherapy-induced stomatitis lasts for 3-12 weeks. RIM-associated symptoms arising during RT/ radiochemotherapy for head and neck cancer include “mouth and throat sores”; difficulty in swallowing; pain; lost or altered taste (dysgeusia); excessive secretions that may lead to gagging, nausea, and vomiting; loss of appetite; fatigue; weight loss; and aspiration. The management of mucositis has already been discussed above.

Oral Pain

Pain management is the single most important aspect of symptom control during HN radiation. The management of Oral Pain due to radiotherapy is the same as management of chemotherapy induced Oral Pain.

Salivary Gland Hypofunction & Xerostomia

Ionizing radiation results in cell damage, death and subsequent fibrosis of the salivary glands. Doses as low as 20 Gy will result in sparse thick ropy saliva. In particular, if the parotid glands are in a field which received 40Gy or over, permanent dysfunction of the salivary glands should be expected and discussed with the patient prior to treatment.^[6]

Management of xerostomia

- Prevention of salivary gland hypofunction and xerostomia

To prevent or reduce the extent of salivary gland hypofunction and xerostomia, parotid-sparing Intensity-Modulated Radiation Therapy (IMRT) is recommended as a standard approach, if oncologically feasible. In addition, treatment should further reduce the radiation dose to the submandibular and minor salivary glands, as these glands are the major contributors to moistening of oral tissues.^[7] Another preventive strategy to reduce radiation-induced salivary gland hypofunction and xerostomia is surgical transfer of one submandibular gland to the submental space not included in the radiation portal. Amifostine is an organic thiophosphate approved for the protection of normal tissues against the harmful effects of radiation or chemotherapy.

- Alleviation of xerostomia

Treatment of salivary gland hypofunction and xerostomia induced by radiation therapy is primarily symptomatic. Alleviation of xerostomia includes frequent sipping or spraying of the oral cavity with water, the use of saliva substitutes, or

stimulation of saliva production from intact salivary glandular tissues by taste/mastication, pharmacological sialogogues, or acupuncture.^[7] Saliva substitutes or artificial saliva preparations (e.g., oral rinses or gels containing hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polyglycerylmethacrylate, mucin, or xanthan gum) are palliative agents that relieve the discomfort of xerostomia by temporarily wetting the oral mucosa.^[7] Sugar-free lozenges, acidic candies, or chewing gum may produce transitory relief from xerostomia.^[7]

- Pharmacotherapy

Pilocarpine is the only drug approved by the U.S. Food and Drug Administration for use as a sialogogue (5-mg tablets of Pilocarpine hydrochloride TID) for radiation xerostomia.

Hypogeusia/ Dysgeusia

Dysgeusia may onset within the first week of head and neck radiation due to a direct toxic effect on taste cells. Permanent taste loss may occur at >6000 cGy, particularly if the tongue is within the volume of tissue radiated. Below this level, recovery usually takes several months.

Oropharyngeal Candidiasis

For patients receiving head & neck radiotherapy alone the weighted prevalence of clinical fungal infection was 7.5% pretreatment, 39.1% during treatment and 32.6% after the end of the radiation therapy.^[8] The most common forms of intraoral candidiasis reported in oncology patients are pseudomembranous and erythematous candidiasis (Fig. 1). Oral candidiasis is often associated with a burning mucosal sensation and taste changes. The management of oral candidiasis includes various topical or systemic antifungal drugs depending on the severity of the disease.

Oral Bacterial Infections

Local infections can lead to sialadenitis, periodontitis, abscesses, pericoronitis, or other causes of ulceration. Empiric treatment with antibiotics are usually adequate; however, periodontal lesions usually need additional debridement. The oral cavity may be the portal of entry for systemic infections. Therefore, chlorhexidine rinses should be considered for these patients.^[9] As radiation may permanently alter the quality and quantity of salivary flow, the cariogenic oral bacteria are permitted to colonize the teeth unchecked. In the absence of a strict and meticulous preventive hygiene regimen, rampant caries typically results. The typical appearance of radiation

caries shows rapidly spreading caries along the neck of the teeth causing amputation of the crown (Fig. 2). Thus prevention of oral bacterial infection is directed towards a regimen of strict oral hygiene, daily fluoride application, carbohydrate restriction and frequent dental follow up.

Oral & Perioral Viral Infections

The risk of oral and perioral reactivation or de novo viral infections is low in head and neck cancer radiation patients. Herpes simplex virus infection is the most common viral infection followed by other Herpesviridae.

Halitosis

Halitosis may be due to compromised oral hygiene during cancer therapy. Further aggravating oral factors can be accumulation of food debris, oral mucositis, oral candidiasis, periodontal infection, salivary gland hypofunction, or tumour growth/necrosis.

Trismus

Trismus is frequent in head and neck radiation patients and may severely impact food intake, speech, and compromise oral hygiene. Following radiotherapy, trismus results mainly due to fibrosis of muscles of mastication. This fibrosis is not apparent immediately following radiation treatment but occurs progressively as mucositis subsides. The clinical management of trismus includes different approaches according to patient's condition, for example, surgery, forced opening of mandible, use of opening devices and modification of prosthesis.¹⁰

Abnormal Facial Development in Pediatric Patients receiving Radiotherapy

Higher radiation doses on the order of 6000-7000 cGy are associated with disturbances of facial growth and associated malformations. The child with these growth disturbances may develop micrognathia, maxillary deficiency, retrognathia, skeletal and dental malocclusion as well as other abnormalities in the facial complex. The management of those long term survivors who manifest these complications involves a team approach involving the dentist, orthodontist, oral and maxillofacial surgeon as part of rehabilitation.

Abnormal Development of the Dentition in Pediatric Patients receiving Radiotherapy

As with many other tissues, radiation has the potential to interfere with normal growth and maturation of the developing dentition. The severity of malformation is dependent on the stage of development at which the teeth are irradiated and the total dose received. Abnormal development in

humans has been observed with a total dose as low as 400 cGy.^[6] Dental abnormalities include crown and root dwarfism, root shortening, incomplete calcification, abnormal curvature of the roots, delayed or arrested eruption, and ankylosis of primary teeth leading to problems of malocclusion, periodontal diseases, early tooth loss, etc (Fig. 3). These problems may require substantial efforts by the general dentist in conjunction with other specialists to restore adequate form and function to the dentition.

Osteoradionecrosis

Osteoradionecrosis (ORN) is a rare condition of nonvital bone in a site of radiation injury (Fig. 4). ORN can be either spontaneous or the result of an insult. Symptoms include, but are not limited to:

1. Pain, swelling, or infection of the gums
2. a sore, or ulcer, in the mouth or on the jaw
3. Trismus
4. Loss of sensation in the area
5. Jaw fracture not related to an accident or other trauma
6. Exposed bone inside the mouth

Management of ORN

Management of ORN is based on prevention that begins with a comprehensive oral and dental care before radiation therapy and a close follow-up post radiation. Medical therapy in treatment of ORN is primarily supportive, involving nutritional support along with superficial debridement and oral saline irrigation for local wounds. Antibiotics are indicated only for definite secondary infection. Hyperbaric oxygen therapy is commonly recommended to prevent ORN, but clinical efficacy is inconclusive. Depending on where osteoradionecrosis develops and how far it progresses, the treatment may vary from sequestrectomy to resection.

ORAL TOXICITY IN HEMATOPOIETIC STEM CELL TRANSPLANTATION PATIENTS

HSCT patients are at risk for development of a wide range of oral toxicities like

- Oral infections: dental caries, endodontic infections, periodontal disease (gingivitis, periodontitis), mucosal infections (i.e., viral, fungal, bacterial), hemorrhage, gingival leukemic infiltrates, Metastatic cancer.
- Acute & chronic GVHD, Xerostomia, Oropharyngeal mucositis, Granulomas/papillomas.
- Neurotoxicity: Dental pain, muscle tremor, Temporomandibular dysfunction.

- Relapse-related oral lesions, Secondary malignancies
- Dental/skeletal growth and development alterations

OROFACIAL PAIN FOLLOWING NONSURGICAL TREATMENT IN CANCER PATIENTS

Post radiation osteonecrosis and bisphosphonate-associated osteonecrosis are recognized oral complications that may cause pain; clinical presentation may include pain, swelling, and bone exposure. Oral Graft-Versus Host Disease represents a local manifestation of a systemic disease post-Hematopoietic Cell Transplant that may result in mucosal and arthritic pain. Viral reactivation of herpes viruses may cause pain. Post-neuralgia may result in chronic pain causing painful dysesthesias in the affected area that may persist for years.

ORAL COMPLICATIONS AND SOCIAL PROBLEMS

The social problems related to oral complications can be the hardest problems for cancer patients to cope with. Oral complications affect eating and speaking and may make you unable or unwilling to take part in mealtimes or to dine out. Patients may become frustrated, withdrawn, or depressed, and they may avoid other people. Some drugs that are used to treat depression cannot be used because they can make oral complications worse.

CONCLUSION

Dental care is an important element of your overall cancer care. Beginning as soon as possible after your cancer diagnosis, your treatment team should involve your regular dentist or a dental oncologist.

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