

Review Article

Chemotherapy and Oral Complications - The Most Neglected Side of Cancer

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Abstract:

Oral complications from radiation to the head and neck or chemotherapy for any malignancy can compromise patients' health and quality of life, and affect their ability to complete planned cancer treatment. In the future, dentists are increasingly likely to find that they have patients in their care who may present before or after cancer treatment requiring urgent dental care. Appropriate preventive regimens and timely oral care can minimise complications and improve quality of life. The present article focuses on managing and preventing oral complications of cancer treatment.

Key words: Cancer, Complications, Dental care, Oral health.

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INTRODUCTION:

The term Chemotherapy (CTX) was coined by Paul Ehrlich in 1990's and was defined as "any treatment for disease with drugs (chemo + therapy). It is one of the major category of pharmacotherapy for medical oncology. Chemical substances, that are given as part of a standard for treatment of cancer are anti-cancer chemotherapeutic agents. Chemotherapy may be given with a curative intent, or it may aim to prolong life or to reduce symptoms. This modalities is frequently used in conjunction with other cancer treatments, such as hormonal therapy, radiation therapy, hyperthermia therapy, surgery.^{1,2}

With over 1.4 million new cases of cancer diagnosed each year and a shift to outpatient management, dentist are more likely see some of these patients in day today practice. Because cancer treatment can affect the oral

tissues, dentist should know about potential oral side effects.^{2,3} Preexisting or untreated oral disease can also complicate cancer treatment. Dentist role in patient management can extend benefits beyond the oral cavity.

Oral complications from radiation to the head and neck or chemotherapy for any malignancy can compromise patients' health and quality of life, and affect their ability to complete planned cancer treatment. For some patients, the complications can be so debilitating that they may tolerate only lower doses of therapy, postpone scheduled treatments, or discontinue treatment entirely. Oral complications can also lead to serious systemic infections. Medically necessary oral care before, during, and after cancer treatment can prevent or reduce the incidence and severity of oral complications,

enhancing both patient survival and quality of life.

Single-Agent Chemotherapy: When in chemotherapy only one drug regime is used at a time

Polychemotherapy: Multiple drugs are used at one time. Also called as Combination chemotherapy

Chemoradiotherapy: The combination of chemotherapy and radiotherapy .

Photochemotherapy: Chemotherapeutic drugs that convert to cytotoxic activity when exposed to light is called or photodynamic therapy.

MECHANISM OF ACTION:

ANTI- CANCER Chemotherapeutic drugs are cytotoxic i.e they target Mitosis (M) phase also known as cell division phase, leading to direct damage to fast-dividing cells. Cancer cells are typically the fastest growing cells in the body. As these drugs cause damage to cells, they are termed *cytotoxic*. Mitosis is prevented either by damage to DNA or by inhibition of the cellular machinery involved in cell division.³

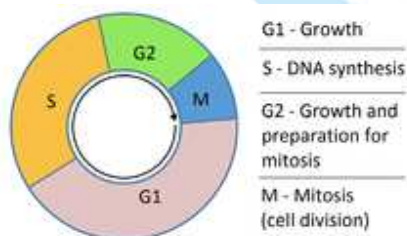


Figure 1: Growth Cycle

As CTx agents act by killing fast dividing cells so unfortunately it also cause damage to normal body cells which have high turnover rate like bone marrow cells ,oral and the gastrointestinal tract, including the mouth, is particularly prone to damage, hair follicle. Most patients being treated for cancer will experience some oral complications. To overcome this damage to normal body cells, targeted therapy has been developed. Newer antineoplastic drugs are

developed which are not selectively cytotoxic for tumor cells and works by targeting abnormally expressed growth proteins.^{2,4} When most people think of the side effects of chemotherapy, hair loss and nausea are usually the first things that come to mind, not dental and oral complications. In addition, chemotherapy often causes a decreased of platelets red and white blood cells; this makes individual more susceptible to infections.

Cancer treatments are often described as stomatotoxic because they have toxic effects on the oral tissues. Oral complications of cancer treatment arise in various forms and degrees of severity, depending on the individual and the cancer treatment. Following are lists of side effects common to both chemotherapy and radiation therapy, and complications specific to each type of treatment.

Oral complications common to both chemotherapy and radiation⁴

- **Oral mucositis⁵:** inflammation and ulceration of the mucous membranes; can increase the risk for pain, oral and systemic infection, and nutritional compromise.
- **Infection⁶:** viral, bacterial, and fungal; results from myelosuppression (decrease in white blood cell count), xerostomia.
- **Xerostomia/salivary gland dysfunction^{5,7}:** dryness of the mouth due to thickened, reduced, or absent salivary flow; compromises speaking, chewing, and swallowing. Persistent dry mouth increases the risk for dental caries.
- **Functional disabilities:** impaired ability to eat, taste, swallow, and speak because of mucositis, dry mouth, trismus, and infection.
- **Taste alterations:** changes in taste perception of foods, ranging from unpleasant to tasteless.
- **Nutritional compromise:** poor nutrition from eating difficulties caused by

mucositis, dry mouth, dysphagia, and loss of taste.

- **Abnormal dental development:** altered tooth development, craniofacial growth, or skeletal development in children secondary to high doses of chemotherapy before age 9.

Specific Complications of chemotherapy:

- **Neurotoxicity:** persistent, deep aching and burning pain that mimics a toothache, but for which no dental or mucosal source can be found. This complication is a side effect of certain classes of drugs, such as the alkaloids.
- **Bleeding:** oral bleeding from the decreased platelets and clotting factors associated with the effects of therapy on bone marrow.

Specific complications of radiation therapy:

- **Radiation caries:** lifelong risk of rampant dental decay that may begin within 3 months of completing radiation treatment if changes in either the quality or quantity of saliva persist.
- **Trismus/tissue fibrosis:** loss of elasticity of masticatory muscles that restricts normal ability to open the mouth.
- **Osteonecrosis:** blood vessel compromise and necrosis of bone exposed to high-dose radiation therapy; results in hypovascularization and decreased ability to heal if traumatized.

Who Has Oral Complications?

Oral complications occur in virtually all patients receiving radiation for head and neck malignancies, in approximately 80 percent of hematopoietic (blood-forming) stem cell transplant recipients, and in nearly 40 percent of patients receiving chemotherapy.⁸ Risk for oral complications can be classified as low or high:

- **Lower risk:** Patients receiving minimally myelosuppressive or nonmyelosuppressive chemotherapy.

- **Higher risk:** Patients receiving stomatotoxic chemotherapy resulting in prolonged myelosuppression, including patients undergoing hematopoietic stem cell transplantation; and patients undergoing head and neck radiation for oral, pharyngeal, and laryngeal cancer.

Dental care before, during and after the therapy is necessary. To avoid or reduce oral problems due to cancer treatment it is important that dental practitioner should follow these tips:

Identifying patients at risk for oral complications:

- Pre-existing oral conditions may increase the risk of infection
- Poor oral care during cancer therapy.
- Calculus and tartar on the teeth
- Broken teeth
- Condition and quality of crowns or fillings
- Periodontal disease
- Appliances such as bridges, partial dentures, or other removable fixtures
- Bacterial and fungal infections

Other risk factors include:

- Type of cancer
- Chemotherapy type and schedule used
- Area irradiated
- Radiation dose
- Decreased blood counts
- Patient's age
- General condition of the patient's health pre-treatment.

The Role of Pretreatment Oral Care^{9,10}

A thorough oral evaluation by a knowledgeable dentist before cancer treatment begins is important to the success of the regimen. Pretreatment oral care achieves the following:

- Reduces the risk and severity of oral complications.

- Allows for prompt identification and treatment of existing infections or other problems.
- Improves the likelihood that the patient will successfully complete planned cancer treatment.
- Prevents, eliminates, or reduces oral pain.
- Minimizes oral infections that could lead to potentially serious systemic infections.
- Prevents or minimizes complications that compromise nutrition.
- Prevents or reduces later incidence of bone necrosis.
- Preserves or improves oral health.
- Provides an opportunity for patient education about oral hygiene during cancer therapy.
- Improves the quality of life.
- Decreases the cost of care.

With a pretreatment oral evaluation, the dental team can identify and treat problems such as infection, fractured teeth or restorations, or periodontal disease that could contribute to oral complications when cancer therapy begins. The evaluation also establishes baseline data for comparing the patient's status in subsequent examinations.

Open communication with the patient's oncologist is essential to ensure that each provider has the information necessary to deliver the best possible care.

Evaluation³

Ideally, a comprehensive oral evaluation should take place 1 month before cancer treatment starts to allow adequate time for recovery from any required invasive dental procedures. The pretreatment evaluation includes a thorough examination of hard and soft tissues, as well as appropriate radiographs to detect possible sources of infection and pathology. Also take the

following steps before cancer treatment begins:

- Identify and treat existing infections, carious and other compromised teeth, and tissue injury or trauma.
- Stabilize or eliminate potential sites of infection.
- Extract teeth in the radiation field that are nonrestorable or may pose a future problem to prevent later extraction-induced osteonecrosis.
- Conduct a prosthodontic evaluation if indicated. If a removable prosthesis is worn, make sure that it is clean and well adapted to the tissue. Instruct the patient not to wear the prosthesis during treatment, if possible; or at the least, not to wear it at night.
- Perform oral prophylaxis if indicated.
- Time oral surgery to allow at least 2 weeks for healing before radiation therapy begins. For patients receiving radiation treatment, this is the best time to consider surgical procedures. Oral surgery should be performed at least 7 to 10 days before the patient receives myelosuppressive chemotherapy. Medical consultation is indicated before invasive procedures.
- Remove orthodontic bands and brackets if highly stomatotoxic chemotherapy is planned or if the appliances will be in the radiation field.
- Consider extracting highly mobile primary teeth in children, and teeth that are expected to exfoliate during treatment.
- Prescribe an individualized oral hygiene regimen to minimize oral complications. Patients undergoing head and neck radiation therapy should be instructed on the use of supplemental fluoride.
- A high-potency fluoride gel, delivered via custom gel-applicator trays, is recommended. Several days before radiation therapy begins, patients should start a daily 10-minute application of a 1.1% neutral pH sodium fluoride gel or a

0.4% stannous fluoride (unflavored) gel. Patients with porcelain crowns or resin or glass ionomer restorations should use a neutral pH fluoride

- For patients reluctant to use a tray, a high-potency fluoride gel should be brushed on the teeth following daily brushing and flossing. Either 1.1% neutral pH sodium or 0.4% stannous fluoride gel is recommended, based on the patient's type of dental restorations.
- Patients with radiation-induced salivary gland dysfunction must continue lifelong daily fluoride applications.

Education¹¹

Patient education is an integral part of the pretreatment evaluation and should include a discussion of potential oral complications. It is very important that the dental team impress on the patient that optimal oral hygiene during treatment, adequate nutrition, and avoiding tobacco and alcohol can prevent or minimize oral complications. To ensure that the patient fully understands what is required, provide detailed instructions on specific oral care practices, such as how and when to brush and floss, how to recognize signs of complications, and other instructions appropriate for the individual. Patients should understand that good oral care during cancer treatment contributes to its success.

Oral Care During Cancer Treatment^{11,12}:

Careful monitoring of oral health is especially important during cancer therapy to prevent, detect, and treat complications as soon as possible. When treatment is necessary, consult the oncologist before any dental procedure, including dental prophylaxis.¹³

- Examine the soft tissues for inflammation or infection and evaluate for plaque levels and dental caries.
- Review oral hygiene and oral care protocols; prescribe antimicrobial therapy as indicated.

- Provide recommendations for treating dry mouth and other complications:
 - Sip water frequently.
 - Suck ice chips or sugar-free candy.
 - Chew sugar-free gum.
 - Use a saliva substitute spray or gel or a prescribed saliva stimulant if appropriate.
 - Avoid glycerin swabs.
- Take precautions to protect against trauma.
- Provide topical anesthetics or analgesics for oral pain.

Schedule dental work carefully: If oral surgery is required, allow at least 7 to 10 days of healing before the patient receives myelosuppressive chemotherapy. Elective oral surgery should not be performed for the duration of radiation treatment.

Determine hematologic status: If the patient is receiving chemotherapy, has the oncology team to conduct blood work 24 hours before dental treatment to determine whether the patient's platelet count, clotting factors, and absolute neutrophil count are sufficient to recommend oral treatment. Postpone oral surgery or other oral invasive procedures if:

- Platelet count is less than 75,000/mm³ or abnormal clotting factors are present.
- Absolute neutrophil count is less than 1,000/mm³ (or consider prophylactic antibiotics).

Consider oral causes of fever: Fever of unknown origin may be related to an oral infection. Remember that oral signs of infection or other complications may be altered by immunosuppression related to chemotherapy.

Evaluate need for antibiotic prophylaxis: If the patient has a central venous catheter, consult the oncologist to determine if antibiotics are needed before any dental treatment to prevent endocarditis.

Follow-up Oral Care Chemotherapy

Once all complications of chemotherapy have resolved, patients may be able to resume their normal dental care schedule. However, if immune function continues to be compromised, determine the patient's hematologic status before initiating any dental treatment or surgery. This is particularly important to remember for patients who have undergone stem cell transplantation. Ask if the patient has received intravenous bisphosphonate therapy.

Radiation therapy¹⁴

Once the patient has completed head and neck radiation therapy and acute oral complications have abated, evaluate the patient regularly (every 4 to 8 weeks, for example) for the first 6 months. Thereafter, you can determine a schedule based on the patient's needs. However, keep in mind that oral complications can continue or emerge long after radiation therapy has ended.

Points to remember

- High-dose radiation treatment carries a lifelong risk of xerostomia, dental caries, and osteonecrosis.
- Because of the risk of osteonecrosis, principally in the mandible, patients should avoid invasive surgical procedures, including extractions that involve irradiated bone. If an invasive procedure is required, use of antibiotics and hyperbaric oxygen therapy before and after surgery should be considered.
- Lifelong daily fluoride application, good nutrition, and conscientious oral hygiene are especially important for patients with salivary gland dysfunction.
- Dentures may need to be reconstructed if treatment altered oral tissues. Some people can never wear dentures again because of friable tissues and xerostomia.

- Dentists should closely monitor children who have received radiation to craniofacial and dental structures for abnormal growth and development.
- Dentists should be mindful about the recurrence of malignancies in patients with oral and head and neck cancers, and thoroughly examine all oral mucosal tissues at recall appointments.^{11,13}

These following complications can result in a significant reduction in the quality of life for the patient.

TASTE PERCEPTION:

"Taste blindness," or an altered sense of taste, is a temporary condition that occurs because of effects on taste buds that are mostly located in the tongue due to chemotherapy of head and neck region.⁵ Common complaints are of food tasting too sweet or too bitter or of a continuous metallic taste. A loss of taste perception makes it more difficult to eat, which leads to weight loss. Taste loss tends to increase in proportion to the aggressiveness of treatment. With time and healing, the sense of normal taste often returns.

Treatment for alterations in taste sensation⁵

1. Eating in relaxed and pleasant surroundings can help reduce problems of altered or lack of taste (taste blindness).
2. Spicy, highly seasoned foods are irritating to many people.
3. Herbs, spices or food seasonings may help. Also, acidic foods such as grapefruit may stimulate taste buds (but avoid them if they irritate your mouth).
4. Experiment with different food textures such as crunchy, creamy, crispy foods.
5. High-protein foods and supplements are particularly important when taste blindness prevents you from eating properly.

If food tastes bitter	If food tastes sweet	If food tastes off
Add sweet fruits or honey to food	Gymnema Sylvestra, a herbal tea deaden taste buds to sweet. Keep in mouth for five minutes	Drinking water, tea, ginger ale or fruit juices mixed with club soda
Replace meat with chicken, eggs, dairy products and fish	Dilute fruit juice or other sweet drinks with half water or ice.	Sugar-free mints of Tic Tacs®. Sugar-free gum or hard candies often reduce after-tastes.
Eat your meal at room temperature. Avoid eating hot food. Mouth care: brushing, mouthwash Diluted Cepacol water mixed with salt, or daily use of Hydrogen peroxide flora or baking soda.	Vegetables may be more appealing	Add wine, beer, mayonnaise, sour cream or yogurt to soups and sauces to disguise the off tastes of other foods. Eat starchy foods such as bread, potatoes, rice and plain pasta.

TABLE 1: Treatment for alterations in taste sensations

Sore Mouth and Throat (Mucositis):⁶

Mucositis is a frequent side effect of chemotherapy. The mouth and digestive tract are composed of cells (mucosa) that are more sensitive to chemotherapy. The lining, or mucosa, of the gastrointestinal tract, which includes the inside of the mouth and throat, is one of the most sensitive areas of the body. Thus, during or after chemotherapy, a cancer patient may present with mouth problems, ranging from dryness to ulcers. Mucositis appears as redness (inflammation), sores (ulcerations) and associated discomfort and pain. Three to ten days following chemotherapy, patients may experience a burning sensation, followed by ulcers. When ulceration develops, treatment is mostly supportive until the cells regenerate themselves, which takes about 7 to 14 days (most commonly associated with a low white blood cell count). The depressant effect of therapy on oral epithelial mitoses can result in thinning and ulceration of the tissues as well as salivary glands. The oral ulcerations may be due to direct cellular cytotoxicity from the chemotherapeutic agents, increased susceptibility to microorganisms owing to neutropenia (bone marrow suppression), trauma, or a combination of these factors. This can impact on oral comfort and nutrition, but adequate care can minimize these effects. Since these changes

(mucositis) are primarily inflammatory, corticosteroid treatment is often helpful.

Systemic: high dose/short course Prednisone 40-80 mg daily orally in one dose (Less than 2 weeks, no taper)¹²

Topical: potent corticosteroids (gel & ointment)

Fluocinonide (Lidex®) 0.05%

Clobetasol (Temovate®) 0.05%

Halobetasol (Ultravate®) 0.05%

- **Mouth Rinse:** elixir dexamethasone 0.5 mg/5ml (1 tsp 3 times daily; hold 1 minute, then spit) Benadry® elixir, lozenges and analgesics may help reduce mouth pain.
- Swishing and gargling the anesthetic gel viscous Xylocaine® 2% can help you eat if you have pain in your mouth, pharynx or esophagus. Use 1 tsp. (5 mL) viscous Xylocaine® before meals (Hold in mouth for one minute, then spit out).
- Cepacol® Lozenge, Chloraseptic spray and lozenges or the use of tea for swishing and gargling may be of some help.
- Frequent use of a gentle mouthwash may help reduce discomfort or pain. A solution of 1 tsp. baking soda and salt dissolved in warm water may be used instead of

commercial mouthwashes, which may be irritating to the oral mucosa.

- Swish diluted milk of magnesia, Carafate slurry or Mylanta around your mouth..
- GI Cocktail - 1 tbsp (15mL) Cherry Maalox® (analgesia) + 1 tsp. (5mL)+Nystatin ®(antifungal)+1/2 tsp. (2mL) Hurricane® Liquid (analgesia) original flavor. Mix ingredients thoroughly. Swish and gargle for one minute, and then swallow immediately before each meal⁽¹³⁾
- Ora balance ,Orabase B ®(OTC) is an adhesive paste with a topical anesthetic (benzocaine) that may be helpful. and also has enzymes that help control oral bacteria.
- Advil, Tylenol and Opioids (such as Vicodin®) are often required to ease pain/discomfort.
- Protective agents such as Sucralfate™ or Kaopectate® are also used to cover ulcers and decrease irritation.

Oral Hygiene¹⁴

To keep patients free from the oral foci of infection and pain to minimize local infection and bacteremia, and to enable them to maintain a nutritious diet is an essential part during chemotherapy.

- A good oral hygiene program includes dental cleaning and scaling, followed by daily brushing and careful flossing to reduce plaque.
- Tooth extractions or repair of cavities should be done before cancer therapy begins.
- Extractions especially should be completed at least two weeks before therapy to give mouth a chance to heal.
- Ill-fitting dentures should be adjusted or replaced. Any periodontal or dental work has to be coordinated with your oncologist.
- Before any dental work is to be performed, blood counts should be checked

- Antibiotics are recommended if white blood cell count is low or there is an infection. Unless there is an emergency, dental procedures should be delayed till the blood counts return to a normal range.

The following daily steps will help your mouth stay in good shape:

1. Use a soft-bristle toothbrush and soften it more by soaking it in warm water. You may find that brushing with a paste of baking soda and water is less irritating than commercial toothpaste. Biotene toothpaste (OTC) is also non-irritating and contains natural salivary enzymes that help control bacteria.^{7,11}
2. If brushing your teeth is painful, use either a cotton swab or Toothettes, a sponge-tip stick impregnated with a dentifrice (toothpaste). A Q-tip dipped in 3% hydrogen peroxide followed by a warm water rinse may help remove debris from around the teeth.
3. Avoid commercial mouthwashes. Some of these have ingredients (especially alcohol) that can irritate your mouth even more. Lemon glycerin swabs may make your mouth feel clean but they are not recommended because glycerin can dehydrate and will make your mouth drier.¹⁵
4. A Water-Pik® to cleanse your mouth is helpful but must be used with caution, since the pressure of the waterjet may irritate tissue.
5. Undiluted chlorhexidine mouth rinses (Peridex ®, Periogard®) may help gum inflammation and bleeding, but contain alcohol and may *sting*. Dilution of these rinses defeats the antibacterial advantages.¹⁶

Infections

Mouth infections can be dangerous. Examine your mouth every day for any irritation or abnormal appearances or feelings. Report any changes to your doctor. If you do get an

infection, it should be treated promptly. Sometimes the diagnosis can be made by clinical characteristics, but may require a smear or cultures.

1. For herpes virus/infection-acute or recurrent¹⁷
 - Acyclovir (Zovirax ®).....400 mg 3/day
 - Famciclovir (Famvir ®).....125 mg 2/day
2. Monilia (thrush Candidiasis) requires antifungal agents.

Systemic

Ketoconazole ® (Nizoral) tabs, 200-400 mg/day Metabolized in liver; to take with food

Fluconazole ® (Diflucan) tabs, 100-200 mg/day Metabolized in kidneys; food elective; saliva level.

Topical (dissolve, swish, swallow)^{17,18}
Clotrimazole (Mycelex ®) oral troches, 10 mg 5/day

Nystatin (Mycostatin ®) suspension, 500,000 u 3/day pastille, 100,000 u 3-5/day powder, 100,000 u/gm (dentures)

Mycolog ® cream (angular cheilitis)

Amphotericin suspension (Fungizone ®) 1 ml (100 mg) 4xd

Freezed nystatin liquid in medicine cups or ice cube trays and let it melt in mouth.

Special Dental Considerations for Hematopoietic Stem Cell Transplant Patients¹⁹

The intensive conditioning regimens of transplantation can result in pronounced immunosuppression, greatly increasing a patient's risk of mucositis, ulceration, hemorrhage, infection, and xerostomia. The complications begin to resolve when hematologic status improves. Although the complete blood count and differential may be normal, immunosuppression may last for up to a year after the transplant, along with the risk of infections. Also, the oral cavity and salivary glands are commonly involved

in graft-versus-host disease in allograft recipients. This can result in mucosal inflammation, ulceration, and xerostomia, so continued monitoring is necessary. Careful attention to oral care in the immediate and long-term post-transplant period is important to patients' overall health.

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