JIACD Continuing Education

Oral Implications of Cancer Chemotherapy

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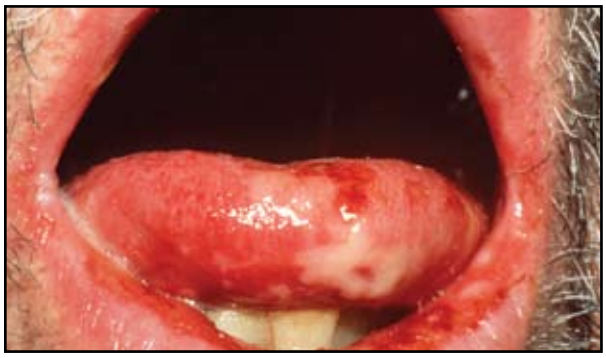
Abstract

Cancer ranks among the leading causes of death in the world today. Although chemotherapy has decreased mortality rates of patients with cancer, the morbidity associated with treatment continues. Initiation and implementation of a comprehensive oral health program that monitors and treats patient before, during, and after chemotherapy is of paramount importance. With optimal coordination of efforts of the entire treatment team, including medical and dental providers, the patient's survival and quality of life will be enhanced. The purpose of this article is to review cancer chemotherapy, its associated complications, and management of the morbidity associated with this treatment.



KEY WORDS: Cancer chemotherapy, oral complications, mucositis, xerostomia, osteonecrosis, management

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Learning Objectives

After reading this article, the reader should be able to:

1. Describe cancer treatment options and the agents involved in chemotherapy.
2. Discuss the dental complications associated with cancer chemotherapy.
3. Identify and manage the dental complications associated with cancer chemotherapy.

INTRODUCTION

Cancer ranks among the leading causes of death in the world today. As dentists we may be called upon to manage patients undergoing cancer therapy. While chemotherapy has decreased mortality rates of patients with cancer, the morbidity associated with the treatment can impair quality of life and interrupt cancer treatment. The goal of dental management for these patients is to prevent the development of oral complications. The oral health team needs to be involved with the patient's treatment before, during and after cancer therapy. The purpose of this article is to review cancer chemotherapy, the complications involved, and management of the morbidity associated with this treatment.

Cancer entails a variety of disease states characterized by the uncontrolled growth and spread of abnormal cells. When this uncontrolled growth is allowed to continue unchecked and untreated, death is likely to occur. 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.[1,2] 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.

In 2005, the American Cancer Society estimated that 1,372,910 new cancer cases would be diagnosed in the United States.[1,3-10] This estimate did not include carcinoma in situ of any site except the urinary bladder, and also did not include basal and squamous cell carcinomas on the skin. It was further estimated that approximately 570,280 Americans were expected to die of cancer in 2005, which equates to more than 1500 people per day. Overall, cancer is the second leading cause of death in the United States accounting for 1 of every 4 deaths, and is exceeded only by heart disease. For all cancer sites combined, African American men have a 25% and 43% higher cancer incidence and mortality rate than white men. For all cancer sites combined, African-American women have lower incidence rates than do white women, but have a 20% higher mortality rate. The five-year survival rate for all cancer sites has increased from 50% in 1974-1976, to 53% in 1983–1985, to 63% from 1992-1999.[3-10]

CANCER TREATMENT AND CHEMOTHERAPY

Cancer is treated by surgery, chemotherapy, radiation therapy, hormones and immunotherapy.[1-3] Surgery is the most common method of treatment for primary tumors and may be curative in well circumscribed tumors. When a primary tumor spreads and metastasizes, radiation therapy and chemotherapy are necessary for definitive care.

Rapidly dividing cancer cells are extremely radiosensitive making radiation therapy an effective adjunct or alternative for the regional treatment of cancer. Chemotherapeutic regimens are used effectively for disseminated cancer and may ultimately provide relief of symptoms, prolong life, and/or cure the disease. It is frequently used in conjunction with surgery and radiation therapy to ensure treatment success, and may be used initially to decrease the size of the primary tumor prior to surgery. Chemotherapy is responsible for the long term survival of patients with hematologic and other malignancies.[11-13] A major advantage of chemotherapy is its ability to treat widespread or metastatic cancer, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas. Chemotherapeutic regimens are intended to destroy rapidly proliferating cancer cells. However, these agents are nonspecific and normal host cells with high mitotic activity may also be adversely affected. Normal tissues that are susceptible to injury by chemotherapeutic agents include the oral and gastrointestinal mucosa, the hematopoietic system, and hair follicles.[12,17,18]

Alkylating Agents. The alkylating agents are considered proliferation-dependent, but cell-cycle phase nonspecific. DNA alkylation can occur anytime in the cell cycle. Examples of alkylating agents used in chemotherapy include: mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide, procarbazine, cisplatin, and oxaliplatin.[12,17,18]

Antimetabolites. These drugs replace the natural building blocks in DNA molecules and may alter the function of enzymes required for cell metabolism and protein synthesis. Additionally, they induce cellular starvation as they mimic nutrients required for cell growth. Antimetabolites are cell-cycle specific and are most effective during the S-phase of cell division. Toxicities associated with these drugs are seen in cells with elevated mitotic activity. Examples of antimetabolites include purine antagonists, pyrimidine antagonists, and folate antagonists such as 6-mercaptopurine, 5-fluorouracil, gemcitabine, and methotrexate.[12,17,18]

Anti-tumor Antibiotics. These are a diverse group of compounds that are cell cycle nonspecific. These agents bind with DNA, preventing RNA synthesis, disrupting protein formation, and ultimately causing cell death. Anti-tumor antibiotics are not the same as antibiotics used to treat bacterial infections. These drugs cause uncoiling of DNA and prevent cell reproduction. These agents are widely used in the treatment of a variety of cancers. Some examples of antitumor antibiotics include: doxorubicin, mitoxantrone, and bleomycin.[12,17,18]

Steroid and Hormonal Agents. These agents include adrenocorticosteroids, estrogens, antiestrogens, progesterones, and androgens. Hormonal agents alter the hormonally dependent intracellular environment of cancer cells. These drugs may act as agonists to activate certain receptors that ultimately inhibit tumor growth. Alternately, they may act as antagonists that compete with natural hormones that promote tumor growth. Although the specific mechanism of action is not entirely clear, steroid hormones modify the growth of certain hormone-dependent cancers. Tamoxifen, for example, is used for estrogen-dependent breast cancer.[12,17,18]

Plant Alkaloids. Plant derived alkaloids are anti-tumor agents that act specifically by blocking cell division during mitosis. They are commonly used in the treatment of acute lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphomas, neuroblastomas, Wilms' tumor, and cancers of the lung, breast and testes. Commonly used plant alkaloids include vincristine and vinblastine.[12,17,18]

Bisphosphonates. As a class, they are divided into two main categories: nitrogenous bisphosphonates and non-nitrogenous bisphosphonates. Bisphosphonates inhibit osteoclast action and are typically used in the prevention or treatment of osteoporosis, osteitis deformans, bone metastasis, multiple myeloma and other conditions featuring bone fragility.

Newer Agents. Nitrosoureas act similarly to alkylating agents and also inhibit changes necessary for DNA repair. These agents cross the blood-brain barrier and are therefore used to treat brain tumors. They are also used to manage lymphomas, multiple myeloma, and malignant melanoma. Carmustine and lomustine are the major drugs in this category. Other newer chemotherapeutic drugs target specific, active proteins or processes in cancer cells, such as receptors, growth factors, or kinases. Because the targets are cancer-specific proteins, the hope is that these drugs will be much less toxic to normal cells than conventional cancer drugs.[17,18]

ORAL COMPLICATIONS

Chemotherapeutic agents are toxic compounds that target rapidly proliferating cells, both malignant and normal. The level and type of toxicity of the regimen depends on the patient, the type of tumor, and therapy-related variables. Patient-related variables include the overall health and immunity of the patient before and during chemotherapy. Therapy-related variables involve the regimen, frequency of treatment, dosage, and route of administration. Fortunately, many normal adult cells do not divide rapidly and are less sensitive to the toxic effects of the chemotherapy. Certain normal cells, however, such as those of the oral and gastrointestinal mucosa, hemopoietic system, and hair follicles divide more rapidly. Thus, the effects of chemotherapy may result in a myriad of oral complications which include: mucositis, pain, infection, hemorrhage, xerostomia, neurologic and nutritional problems. It is extremely important to anticipate and recognize the conditions that predispose patients to complications so that they can be prevented or minimized by proper management before, during, and after chemotherapy.[12]

Mucositis

Mucositis is the inflammation of the mucous linings of the digestive tract which can lead to frank ulceration. It is the most common oral complication associated with the use of chemotherapeutic agents, occurring in approximately half of the patients undergoing chemotherapy.[12,13,19-21] When both chemotherapy and radiation therapy are used concomitantly, the incidence of mucositis increases to 80-90%.[13,23] It is both a painful and debilitating condition that is a dose and rate-limiting adverse effect of chemotherapy. 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. [58] Mucositis can be assessed clinically and with subjective input from the patient.

Table 1: The WHO Mucositis Scale	
Grade	**Clinical Presentation**
0	**Normal**
1	**Soreness with or without erythema**
2	**Ulceration and erythema**
3	**Ulceration and erythema, patient cannot swallow solid food**
4	**Ulceration/pseudomembrane formation of such severity that feeding is not possible**

The World Health Organization (WHO) mucositis scale combines the objective and the subjective into a useful grading system (Table 1).

Pain is the most frequent symptom resulting from chemotherapy-induced mucositis. Another notable concern is the susceptibility to infection from normal oral flora and transient microorganisms due to breakdown of the mucosal barrier. In addition to the chemotherapeutic regimens, certain patient variables may influence the incidence of mucositis such as age, nutritional status, oral hygiene, oral microflora, salivary function, and immunologic function.[12,13,19]

The current working biological model for mucositis is based on 5 phases: initiation, message generation, signal amplification, ulceration, and healing phase. In the initiation phase, the chemotherapeutic agents cause cellular damage directly and indirectly via the generation of free radicals. In the message generation phase, transcription factors are activated, which induce the release of pro-inflammatory cytokines and tumor necrosis factors. The resulting inflammation ultimately increases the concentration of chemotherapeutic agents at the site. During the signal amplification phase, positive feedback loops are activated which contribute directly to cellular and tissue injury. The result is erythema and epithelial atrophy 5 days after the initiation of chemotherapy. Ulceration can be induced by trauma from day-to-day activities, such as speech, swallowing, and mastication. Bacteria within the ulcers produce endotoxins in the mucosal tissues. This ulceration phase is most responsible for the pain and decreased food intake associated with mucositis. During the fifth and final healing phase, cell proliferation occurs with re-epithelialization of ulcer. Reconstitution of the white blood cells regains local control of bacteria, which also contributes to resolution of the ulcer.[21,24]

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 patients and correlates with a normal white blood cell count.[19,24] 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 (Figure 1). Peripheral erythema is usually present. Ulcers may range from 0.5 cm to greater than 4 cm in maximum dimension. Mucositis pain results in difficulty opening the mouth, dysphagia, and difficulty with oral hygiene.[19,21,24]

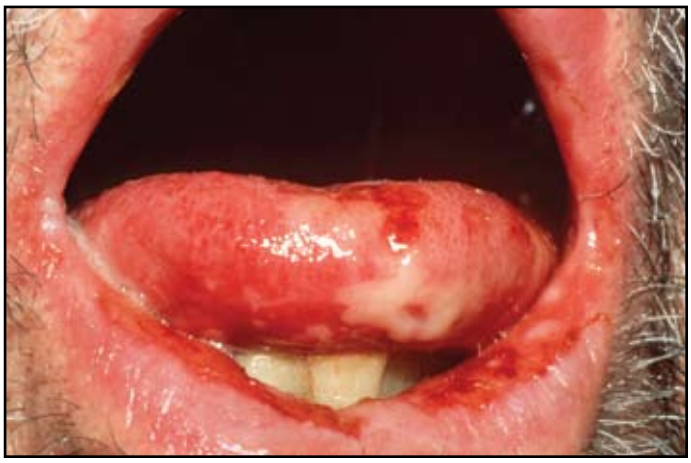

Figure 1: Patient presenting with mucositis during chemotherapy.

Management. Treatment is primarily empirical and designed to improve patient comfort and to minimize infections. Though much research has been dedicated to this topic, results are difficult to interpret. The grading of mucositis is not consistent study to study, and many protocols were not placebo-controlled. With this in mind we begin by discussing mucositis prevention. 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.[39,53] Cryotherapy is thought to reduce blood flow to the oral mucosa, minimizing exposure to the toxic effects of chemotherapy. Recent attention has been given to keratinocyte growth factors (KGF) such as palifermin in oral mucositis prevention for hematologic cancers.[54-55] KGF is protective of epithelial tissues and one study showed that palifermin given for three consecutive days (60 µg/ kg) before total body radiation and high dose chemotherapy resulted in a 35% reduction in WHO grade 3 or 4 mucositis, decreased mucositis duration from 9 to 3 days, and resulted in fewer incidents of febrile neutropenia compared to placebo. 55 Side effects included rash and taste alteration. Further studies are needed to assess KGF usefulness and safety in other forms of malignancy.

Immediately after chemotherapy, a baseline mucositis grading should be performed and repeated once a day until resolution. The provider should also assess for pain, nutrition, and saliva production. An essential part of the oral care is the frequent and liberal use of a mouthrinse for the removal of debris.[37] When selecting a mouthrinse, avoid those containing alcohol, phenol, aromatics, astringents, oils, and antiseptics. A sodium bicarbonate rinse of one-half teaspoon of saline and one-half teaspoon of baking soda in sixteen ounces of water reduces acidity, dilutes accumulating mucus, and minimizes yeast colonization. Avoid products irritating to the oral tissues such as alcohol, tobacco, spicy and course foods, high acid containing foods and beverages and refrain from using removable prostheses[20,23.37]

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.[38] These topical agents are frequently combined with coating agents such as kaolin with pectin (Kaopectate), magnesium hydroxide or aluminum hydroxide (Milk

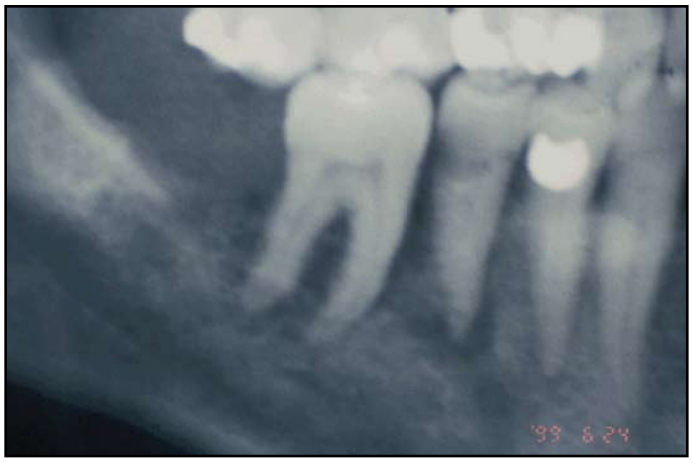

Figure 2: Radiograph suggests presence of periapical infection with possible spread to adjacent bone.

of Magnesia, Mylanta) to prolong patient comfort. The KLB suspension is available on most hospital formularies and consists of equal parts kaolin, viscous lidocaine, and diphenhydramine (Benadryl). Patients need to be counseled that these agents may initially burn upon application, increase the risk of self-induced trauma, decrease taste acuity, and interfere with swallowing that could lead to aspiration by depression of the gag reflex.[19] Low-level laser therapy (LLLT) has found to be stimulating on epithelial cells. Advances in LLLT have shown efficacy both as a treatment to heal ulcers and as a preventive measure for mucositis.[56-57] If systemic analgesia is necessary, acetaminophen or opioids in combination with acetaminophen are the most appropriate.[19] Preparations also available in elixir form for easier swallowing.

Infection

Bacterial infections dramatically contribute to morbidity and mortality in patients receiving chemotherapy and oral sources account for 25 to 50% of the infections in these patients.[23] Chemotherapy-related oral infections may involve the teeth, gingiva, salivary glands, or mucosa (Figure 2).[12] It is of paramount importance to remember that the cardinal signs of infection are not always present in the myelosuppressed patient. Erythema and swelling may not be present, therefore monitoring for more reliable indicators such as fever, pain, and the presence of lesions is necessary. Coagulase-negative *staphylococci* and *streptococci* oral flora are other common sources of infection in myelosuppressed individuals.[13,19,23] Additional opportunistic microorganisms that cause infections include: *Klebsiella pneumonia, Pseudomonas aeruginosa*, and *Escherichia coli*.[12,13,25] When the patient's granulocyte count falls below 1,000 mm^3, pathogenic microorganisms found subgingivally or in the periradicular area may cause acute exacerbations of pre-existing periodontal or periradicular infections.[13,26]

Brushing teeth 2 to 3 times a day and daily flossing should be continued during chemotherapy as the increased risk of infection associated with inadequate oral hygiene may outweigh the increased risk of bleeding.[19] However during the thrombocytopenic phase of chemotherapy, a modified mechanical approach using a piece of gauze, or cotton swab with a topical antimicrobial agent such as chlorhexidine or povidone iodine solutions, may be prudent.

Should an acute odontogenic infection arise during this period that may require dental intervention, consultation with the primary care physician is needed to determine the patient's ability to tolerate dental care. Furthermore, even if there is no infection present, but emergency dental care needs to be provided, the need for antimicrobial prophylaxis should be determined based on the patient's white blood cell count (WBC). A WBC under 2,500/mm^3 or an absolute neutro-

phil count of less than 500/mm^3 warrants antimicrobial prophylaxis before dental procedures that produce bleeding and lead to bacteremia.[59-60]

Fungal infections can be one of the most dangerous complications for the chemotherapy patient. The most common infection is from *Candida sp.*[13,23] Systemic fungal infections have a higher mortality rate than any other infection in the myelosuppressed patient. The majority of systemic fungal infections are believed to originate from the oral cavity.[13] Under normal conditions, *C albicans* growth is inhibited by other microorganisms such as *Lactobacillus acidophilus*, and an intact immune system. Both these inhibitors are altered during chemotherapy.

Clinically, *C albicans* infection, or candidosis, may present in several forms. The lesions are either a white or a red patch, and are either acute or chronic. In the myelosuppressed, low grade chronic infections can have acute exacerbations. Acute pseudomembranous candidosis, is an infection of the superficial layers of the oral mucosa (Figure 3). It presents as a white plaque which can easily be rubbed off. Removal of the pseudomembrane reveals a raw, red ulcer or area of erythema. There may be a burning symptom reported. Acute atrophic candidosis is a raw, red, painful patch. It lacks a pseudomembrane. Chronic atrophic candidosis includes angular cheilitis and denture stomatitis. Ill fitting or porous maxillary denture bases are sources of chronic irritation and serve as a nidus for *C albicans*. Angular cheilitis is an infection of the corner of the mouth occasionally with a Staphylococcus species co-infection. Chronic hyperplastic candidosis is a white patch that does not rub off, characterized by deeper invasion of the mucosa.

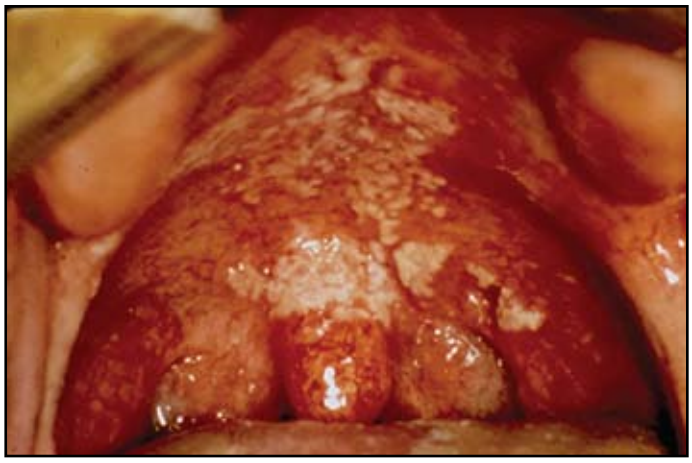

Figure 3: Patient presenting with oral candida infection post chemotherapy treatment.

Management. Due to the increased morbidity and mortality associated with fungal infections and the difficulty with early diagnosis, any superficial evidence of fungal infection in the oral cavity or oropharynx necessitates immediate aggressive intervention to prevent systemic spread.[40] Fluconazole is the most reliable and frequently recommended prophylactic agent to prevent oropharyngeal candidosis in the myelosuppressed patient.[40] A loading dose of two 100 mg tablets of Fluconazole followed by one tablet per day should be continued for 2-3 weeks. Fluconazole is not effective against *Aspergillus* species and some resistant *Candida* species. Itraconazole and Ketoconazole may be used for resistant cases with Amphotericin B as the drug of last resort. For patients with dental prostheses, dentures can be left out of the mouth or treated with nystatin ointment or powder inside the denture base after it is cleaned at each meal.

Viral infections most commonly seen in the chemotherapy patients include the herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV). These herpes fam-

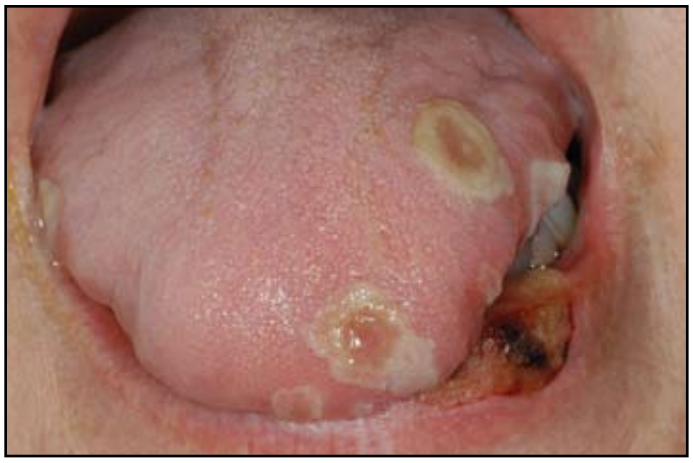

Figure 4: Outbreak of CMV during chemotherapy.

ily viruses are known for their latency stage following primary infection and can be reactivated during immunosupression.[27] The incidence of recurrent HSV infection has been shown to occur in 48% of the patients undergoing chemotherapy.[28] HSV recurrence may appear 7 to 14 days following administration of chemotherapy.[27,28] The severity of the case is directly related to the degree of immunosuppression.[27] Recurrent HSV lesions can be found on the lip or on keratinized gingival or palatal surfaces as a small cluster of vesicles that rapidly ulcerate and coalesce. The condition is self-limiting and resolves in 2 weeks.

Recurrent VZV infection is termed herpes zoster or shingles. It can occur on any dermatome of the body. When it occurs within the trigeminal dermatome, lesions can be found on the face or intraorally. They follow and stay confined to their respective trigeminal divisions. Characteristically they abruptly halt at the midline. As in HSV, intraoral VZV recurrence is confined to keratinized tissues. In the chemotherapy patient, herpes zoster manifests several weeks after completion of chemotherapy. In immunosuppressed patients, an atypical widespread distribution may occur. Lesions are painful and may last several weeks.

CMV infections result in a fever that resolves in 3 to 5 days. The most common clinical findings involve esophagitis, gastritis, colitis, hepatitis, pneumonitis, and retinitis. Intraoral CMV infections may present as irregular pseudomembranous ulcerations with a granulomatous base (Figure 4). Dissemination of CMV may occur and such infections are often fatal in immunosuppressed patients.[29]

A number of oncology treatment centers recommend prophylactic antiviral agents in the patient with evidence of previous viral exposure.[19,26,27,29] For HSV seropositive patients undergoing stem cell transplantation, intravenous acyclovir administration is the standard of care to reduce the risk of recurrent infection and to treat mucocutaneous infection.[27,29] For patients with less severe myelosuppression, oral acyclovir, famciclovir, or valacyclovir may be effective. The famciclovir oral regimen for HSV is 500 mg bid for seven days.

Clinical findings reveal that antiviral prophylaxis for recurrent VZV is not effective and only delays reactivation and increases development of resistance. Initial therapy for herpes zoster with valacyclovir is 1,000 mg tid for seven days. For treatment of resistant HSV and VZV, foscarnet is the drug of choice. Either foscarnet or ganciclovir are recommended in the prophylaxis and treatment of CMV.[27]

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 thrombocy-

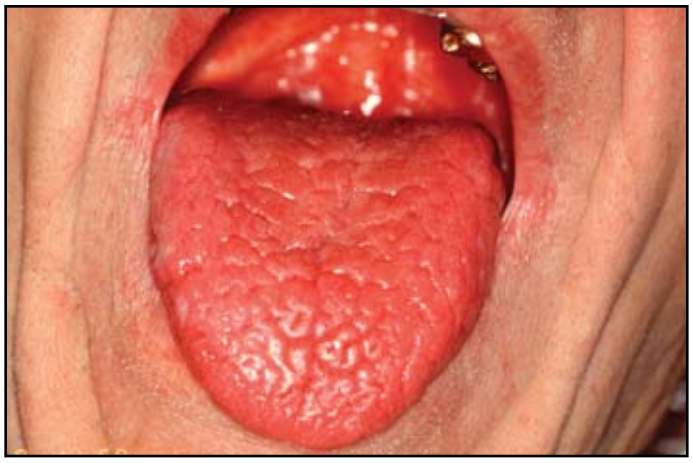

Figure 5: Patients often present with beefy red tongue from xerostomia.

topenia (<20,000 mm^3) is responsible for these changes, however qualitative platelet characteristics are also altered during chemotherapy.[12,30-33]

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.[12,31] 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.

Management. 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 mm^3, conventional oral hygiene may be too traumatic.[26] 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 mm^3. 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]

Xerostomia

The subjective report of a dry mouth is xerostomia. It may be real or perceived. Although only a small number of chemotherapeutic agents cause xerostomia, the effect may be devastating when it occurs in conjunction with an existing mucositis. Alterations in salivary flow and may predispose the patient to oral candidosis, dysphagia, and malnutrition. Reduced amounts of salivary amylase and IgA levels may result in increased incidence of oral infections by opportunistic microorganisms.[13,34] Also, the salivary secretion of chemotherapeutic agents may contribute to the incidence of mucositis.[19] Xerostomia may also be influenced by the patient's hydration levels and medications. The most common medications known to cause xerostomia are diuretics, antihistamines, antipsychotics, beta blockers, and tricyclic antidepressants.

A decrease in saliva causes the oral mucosa to appear shiny, atrophic, and desiccated (Figure 5). Lack of saliva promotes the accumulation of bacteria, plaque, and material alba, which increases the patient's susceptibility to caries and

periodontal disease. Lipstick sticking to the teeth and the tongue sticking to the intraoral mirror are signs of a dry mouth. Milking the parotid gland for saliva or observing its build up in the floor of the mouth are other measures to assess salivary flow. Better saliva measurement techniques are available such as the use of a Carlson-Crittenden cup to measure parotid salivary flow, but they are not utilized much outside the research setting.

Management. Chemotherapy-induced xerostomia is usually of short duration and normal salivary function frequently returns several months after completion of chemotherapy. During chemotherapy, patients may manage dry mouth by frequently sipping on water, ice chips, and chewing xylitol-containing gum. Other measures would be those that conserve hydration. Avoiding smoke tobacco, alcohol based mouthwashes and beverages, caffeine, and mouth breathing. A humidifier by the bedside may also be of value at night time. A number of over the counter saliva substitutes, moisturizers, and stimulants are available for patient use. The saliva substitutes are predominantly carboxymethylcellulose-based and although they provide viscosity, they are inadequate substitutes for saliva. Biotene oral products, such as toothpaste, chewing gum, and mouthwash used in combination with oral lubricant may mimic the actions of saliva and have found acceptance by a number of patients.[41] Alternative treatments such as acupuncture and electric stimulation of the salivary glands have shown limited success and acceptance.[62-63]

When local measures are insufficient, the parasympathomimetics like pilocarpine 5 mg taken 3-5 times daily has shown success when used in radiation-induced xerostomia and is effective in patients that have reduced salivary gland function.[63] Common side effects, except for the sweating, are usually mild and include headache, rhinorrhea, increased lacrimation, and urinary frequency. A newer medication is cevimeline which does not bind as strongly to muscarinic receptors on sweat glands and thus is an improvement over pilocarpine.[64] It is a 30 mg tablet taken tid.

Neurological Problems

Chemotherapy-induced neuropathy may be characterized by pain or paresthesia, especially with the administration of plant alkaloids such as vincristine, vinblastine, and etoposide.[12,13,30,31,35] Other agents capable of causing neuropathy are altretamine, carboplatin, cisplatin, cladribine, docataxel, oxaliplatin, paclitaxel, procarbazine, and thalidomide.[18,36] Neurological symptoms frequently disappear after the chemotherapeutic agent is discontinued.[12,31] Therefore, the diagnosis of oral pain may be challenging because the symptomatology may be either quiescent or aggravating, depending on the stage of chemotherapeutic regimen.

Bisphosphonate-Induced Osteonecrosis

Although the class of drugs known as bisphosphonates are not anti-cancer chemotherapy drugs because they are not cytotoxic to cancer cells, they nevertheless produce a serious side effect limited to the jaws: bisphosphonate induced osteonecrosis of the jaws (BIONJ).[43] The mechanism of their therapeutic value is the same as their toxic effect. That is, they induce apoptosis (cell death) in normal osteoclasts and osteoclast precursors.[44, 45]

Two drugs associated with BIONJ are pamidronate (Aredia), usually given intravenously at 90 mg monthly, and zoledronate (Zometa) usually given at a dose of 4 mg monthly. Their indi-

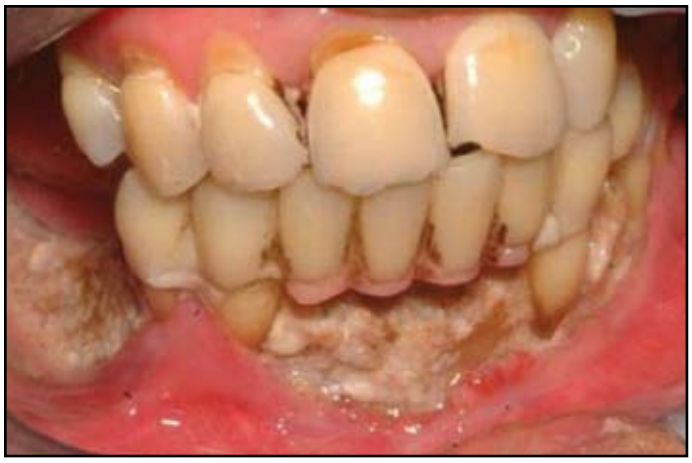

Figure 6: Significant spontaneous bone exposure (BIONJ) in a patient who received intravenous Zometa therapy for four years.

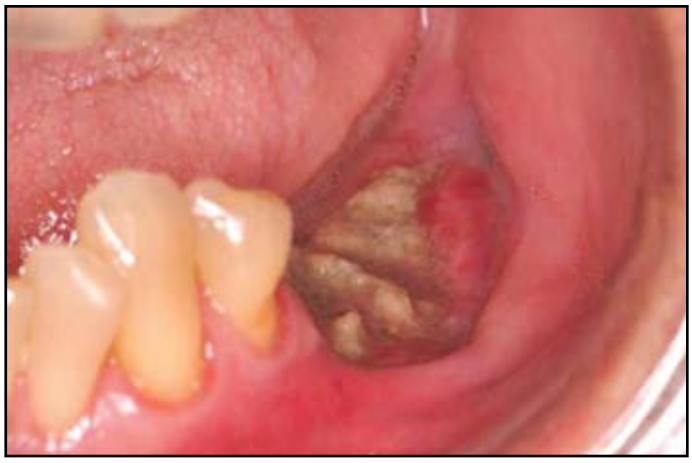

Figure 7: Significant post extraction bone exposure (BIONJ) in a patient who received intravenous Zometa therapy for four years.

cation is to limit the bone resorption of metastatic cancer deposits in bone and to lower serum calcium levels in hypercalcemia of malignancy.

The toxicity of intravenous bisphosphonates results from depleting the osteoclast population and the osteoclast precursors in bone marrow so that normal bone turnover, which is important to bone maintenance and bone renewal, is severely suppressed. Since most bisphosphonates have a half life in bone of over 11 years,[47] their bone toxicity is related to the length of time which the patient has taken the medication. For intravenous bisphosphonates, such toxicity begins at about the fifth dose and increases thereafter. The jaws are targeted because of their rapid turnover[48,49] and, therefore, depend more significantly on osteoclastic function than any other bone in the adult skeleton. As such, diseases or interventions that require elevated levels of bone turnover such as periodontal disease, tooth extractions, and implant placements are known to precipitate BIONJ expressed clinically as exposed nonhealing bone[50].

Since its initial description in 2003,[51] over 4,000 cases of intravenous BIONJ have been reported to the United States Food and Drug Administration (FDA). In addition, the profession has learned important lessons about BIONJ and has developed reasonable protocols to prevent many cases and manage this drug complication.

The primary lessons learned are that minor office-based debridements of BIONJ typically result in additional bone exposure and should be avoided. Secondary bacterial colonization and direct infection of exposed bone typically incite pain. Because of the long half life of bisphosphonates in bone, discontinuation of intravenous bisphosphonates does not result in healing of the bone. Almost 25% of cases occur spontaneously, indicating that these are unlikely to be prevented by dental means and are instead due to the length of time over which a patient has received the drug (Figure 6).[52] About 75% of cases are a result of a surgical procedure in the either the maxilla or mandible (Figure 7) which suggest that many cases are preventable by preventative dental care and periodontal mainte-

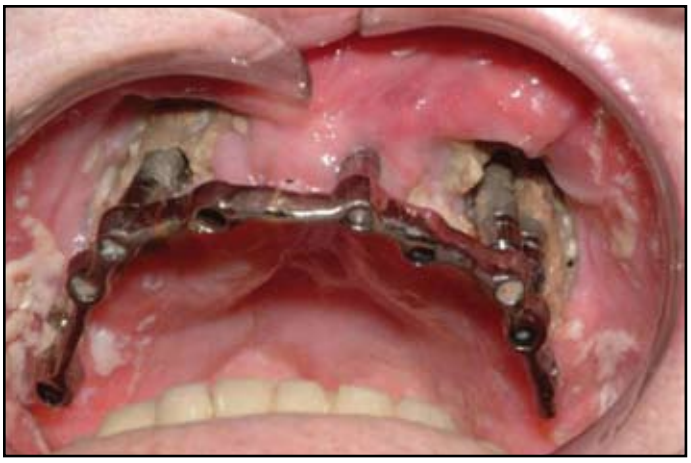

Figure 8: Dental implant placements in individuals who have already received intravenous bisphosphonates posses a significant risk for the development of BIONJ.

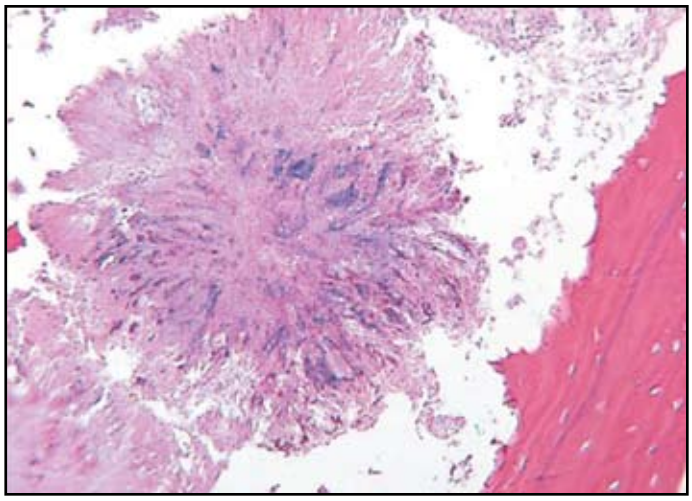

Figure 9: Colony of *Actinomyces* with *Eikenella* on the bone surface of a patient with BIONJ.

nance.[52] Active periodontal disease and healing extraction sockets are the two most consistent inciting events due to the rapid turnover of bone.

Management. Since intravenous bisphosphonates accumulate in bone rapidly and risk of BIONJ may be realized after as little as five doses, it is best to begin dental preventative measures prior to or within the first three months of bisphosphonate administration.52,47 It would be ideal for the dental profession to develop a closer working relationship with the medical oncologists who prescribe these drugs in their treatments and gain referrals prior to therapy or at the start of therapy. During this time, unsalvageable teeth should be removed first and then followed by any required periodontal surgery and maintenance. This should be followed by endodontic, restorative and prosthodontic care aimed at stabilizing the dentition and reducing the need for extractions, periodontal surgeries, and other procedures that may require bone healing and regeneration. Although not well studied, dental implant placements are thought to pose a much higher risk for BIONJ (Figure 8) Adult orthodontics should only be considered with caution.

After five doses of intravenous bisphosphonates, its accumulation in bone increases BIONJ risk. Therefore, after the fifth dose, surgical procedures in the jaws should be avoided if possible. Discontinuing intravenous bisphosphonates does not seem to significantly reduce the risk for BIONJ. It is preferable to treat nonrestorable teeth with root canal therapy and crown amputation rather than risk BIONJ from an extraction. By the same token, mobile teeth that are not abscessed and have a reasonable amount of bone around their root surfaces are best splinted than extracted. If teeth are abscessed with no options other than extraction, it should be accomplished with informed consent describing the high likelihood of exposed bone that will not heal and may result in a fracture or the need for resective surgery.

The treatment goals in cases of BIONJ are infection control, pain control, and limitation of extension. This is based on the experience that only major jaw resections can predictably

resolve BIONJ and that due to their cancers and/or their cancer therapies many are not good candidates for extensive surgery. Instead, it has been found that 89% of such patients can be managed to a pain free state with adequate function with the use of antibiotic regimens and a 0.12% chlorhexideine rinse.[52]

Because the four most common microorganisms seen in BIONJ are *Actinomyces, Moraxella, Eikenella,* and *Viellonella* (Figure 9), the most useful antibiotic for the treatment of BIONJ is oral phenoxymethyl penicillin (penicillin V-K) 500 mg. Penicillin VK 500 mg four times daily combined with 0.12% chlorhexidine (Peridex) oral rinses three times daily is baseline therapy. Due to the lack of human toxicity of penicillin VK and its long term gastrointestinal tolerance it has been used continuously over many months and even years. That is, after an initial control of pain at four times daily a twice daily maintenance schedule can be used. However, if the referring physician or the patient expresses a concern about long term antibiotic use, the penicillin VK may be limited to use only at the time of pain recurrence. Clindamycin is not recommended due to its reduced or even total lack of activity against these organisms.

If the patient is penicillin allergic, levoflaxacin (Levaquin) 500 mg once daily, clarithromycin (Biaxin) 500 mg twice daily or doxycycline (Vibramycin) 100 mg twice daily are useful second choices. However, these antibiotics each have their own toxicity and are best used as 21-day courses at times of painful episodes. If the patient has a minimal response to any of these baseline antibiotic regimens or has frequent exacerbation, the addition of metronidazole (Flagyl) 500 mg three times daily has shown to be very useful. Patients that are refractory to these regimens with frequent or painful episodes or who develop a pathologic fracture are candidates for a resection.

Resections of the mandible for refractory cases have been necessary in only 13 of 134 (10%) of patients in our experience.[52] In each case, the BIONJ was resolved and did not recur. With resections of the mandible, immediate or even delayed reconstruction with bone grafts is a risk and has not been adequately explored. Rigid titanium plate reconstruction has been the mainstay in retaining jaw continuity, form, and function without infections or plate exposures. In maxillary resections, a prosthodontist should be consulted to provide an obturator appliance as is done for maxillary cancer resections.

Nutritional Problems

Chemotherapy-induced mucositis may significantly impair the patient's nutritional and caloric intake. Further compromising the patient's nutritional status is chemotherapy-induced nausea, vomiting, diarrhea, anorexia, enteritis, malabsorption, and impaired liver function. The diet during mucositis is tailored to the patient's ability to eat solid foods. If chewing is too painful, a liquid diet can be prescribed. Food that would take shape of its container would be characterized as a liquid (broth, pudding, mashed potatoes, baby food). If the patient is unable to tolerate liquids, total parenteral nutrition will be prescribed.

SUMMARY

Chemotherapy patients may experience acute and chronic oral complications. The severity of oral complications may necessitate modification or cessation of the chemotherapy regimen, negatively impacting patient survival. Thus, the oral healthcare provider plays an important role in the multi-

disciplinary approach for overall treatment of these patients. The goal of the oral healthcare provider is to minimize, to the extent possible, interruption of chemotherapy from dental and oral complications.

Ideally, prior to chemotherapy, patients should undergo a thorough oral examination to include both a clinical and radiographic evaluation. Even if chemotherapy must begin immediately or has already commenced, this examination provides a baseline for comparison and assists in the monitoring and treatment of oral complications. It also serves to rule out any tumor metastases to the mouth or jaws. Ultimately, the effect of the chemotherapy on the patient's oral health is unpredictable and close follow-up is necessary.

Time and hematologic status permitting, potential sources of infection and irritation should be treated and minimized at this time. Initially, the patient should receive a dental prophylaxis. Any teeth deemed unrestorable or those with severe periodontal involvement should be extracted. Any endodontically involved teeth should be treated via root canal therapy or extracted. In an ideal situation, all surgical procedures should be completed at least 10 days prior to the onset of neutropenia.[12,13,31]

Post-chemotherapeutic dental management of the patient is essential. In most cases, previously postponed dental procedures can now be completed. It is important to continually monitor the patient and to reinforce proper oral homecare. Post-treatment dental care should be directed at minimizing recurrence of dental disease, providing palliation, and improving the patient's quality of life.

Although chemotherapy has decreased mortality rates of patients with cancer, the morbidity associated with the treatment continues. Initiation and implementation of a comprehensive oral health program that monitors and treats the patient before, during and after chemotherapy is of paramount importance. With optimal coordination of efforts of the entire treatment team, the patient's survival and quality of life will be enhanced.

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Disclosure:
The opinions and assertions contained in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Department of the Navy, Department of Defense or the US Government.

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Continuing Education JIACD Quiz #1

1. External etiologic factors of cancer include all the following except:
- **a.** tobacco
- **b.** alcohol
- **c.** chemicals
- **d.** hormones

2. Cancer is treated by:
- **a.** surgery
- **b.** chemotherapy
- **c.** radiation therapy, hormones, and immunotherapy
- **d.** All of the above

3. Which agents bind with DNA, preventing RNA synthesis, disrupting protein formation, and ultimately causing cell death?
- **a.** Anti-tumor Antibiotics
- **b.** Antimetabolites
- **c.** Alkylating Agents
- **d.** Plant Alkaloids

4. Mucositis is the inflammation of the mucous linings of the digestive tract which can lead to frank ulceration.
- **a.** true
- **b.** false

5. KLB suspension is used in the treatment of which of the following?
- **a.** infections
- **b.** candida
- **c.** mucositis
- **d.** osteonecrosis

6. Viral infections most commonly seen in chemotherapy patients include all the following except:
- **a.** herpes simplex virus
- **b.** varicella zoster virus
- **c.** rhinovirus
- **d.** cytomegalovirus (CMV)

7. Systemic fungal infections have a low mortality rate in myelosuppressed patients.
- **a.** true
- **b.** false

8. The most common medications known to cause xerostomia include all the following except:
- **a.** diuretics
- **b.** antihistamines
- **c.** antibiotics
- **d.** beta blockers

9. The treatment goals in cases of BIONJ are infection control, pain control, and limitation of extension.
- **a.** true
- **b.** false

10. Commonly used plant alkaloids include
- **a.** Valium
- **b.** Tamoxifen
- **c.** Vincristine
- **d.** Zoledronate

Continuing Education JIACD Quiz #1

11. Internal factors of cancer include:
a. inherited mutations
b. hormones
c. immune conditions
d. All of the Above

12. Cancer is caused by the malfunction of genes that control cell growth, division, and maturation.
a. true
b. false

13. Chemotherapy is responsible for the long term survival of patients with hematologic and other malignancies.
a. true
b. false

14. A major advantage of surgery and radiation is the ability to treat widespread or metastatic cancer, whereas chemotherapy is limited to treating cancers that are confined to specific areas.
a. true
b. false

15. Nitrosoureas act similarly to alkylating agents and also inhibit changes necessary for:
a. RNA repair
b. DNA transcription
c. DNA repair
d. mRNA transcription

16. Chemotherapy-induced neuropathy may be characterized by pain or paresthesia.
a. true
b. false

17. Which of the following contributes to cancer chemotherapy induced nutritional complications?
a. nausea
b. diarrhea
c. impaired liver function
d. All of the above

18. Prevention is the key to controlling hemorrhage.
a. true
b. false

19. KLB suspension is available on most hospital formularies and consists of equal parts kaolin, viscous lidocaine, and diphenhydramine (Benadryl).
a. true
b. false

20. Common microorganisms seen in BIONJ include all of the following except:
a. Actinomyces
b. E. Coli
c. Moraxella
d. Eikenella