Chemotherapy Agents and Dentistry

John H. Hardeman, MD, DDS

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The therapy for any particular type of cancer is becoming more and more sophisticated, and patients are living longer and are even surviving these ordeals. Chemotherapy is a broad term and is oftentimes used to relay the information that the patient is taking medication to combat a particular disease process. Typically this is a cancer. By definition, then, chemotherapy is the treatment of disease by the use of chemical substances, especially the treatment of cancer, by cytotoxic and other drugs.

CLASSIFICATION OF CHEMOTHERAPY AGENTS
Chemotherapy drugs can be divided into several groups based upon various factors, such as the following: how they are formulated, their mechanism of action, specific types of cell that they attack, and their relationship to another drug. Some drugs act in more than one way and may belong to more than one group.

Understanding the mechanism of action of these drugs is important for utilizing them effectively and for predicting their side effects. This understanding helps the treating physicians decide which drugs are likely to work well together, especially if more than one drug will be used in a treatment regimen.

Along with corticosteroids, there are 5 main classes of chemotherapeutic agents: alkylating agents, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, and mitotic inhibitors (Table 1). An in-depth look at each of these classes is warranted to glean a complete understanding of these medications. A summary can be taken directly from the American Cancer Society.

Alkylating Agents
Alkylating agents directly damage DNA (the genetic material in each cell) to keep the cell from reproducing. These drugs work in all phases of the cell cycle and are used to treat many different cancers, including leukemia, lymphoma, Hodgkin’s disease, multiple myeloma, and sarcoma, as well as cancers of the lung, breast, and ovary.

Alkylating agents are divided into different classes and include the following drugs:
- Nitrogen mustards: Cyclophosphamide (Cytoxan)
- Nitrosoureas: Carmustine and Lomustine
- Alkyl sulfonates: Busulfan
- Triazines: Dacarbazine and Temozolomide
- Ethylenimines: Thiotepa and Altretamine (hexa methylmelamine).

Antimetabolites
Antimetabolites interfere with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA. These agents damage cells during the S phase, when the cell’s chromosomes are being copied. They are commonly used to treat leukemias and cancers of the breast, ovary, and the intestinal tract. Examples of antimetabolites include: 5-fluorouracil, 6-mercaptopurine, Capetitabine (Xeloda), Cytarabine, Floxuridine, Fludarabine, Gemcitabine (Gemzar), Hydroxyurea, Methotrexate, and Pemetrexed (Alimta).

Antitumor Antibiotics
These antibiotics are not like the antibiotics used to treat infections. Instead, these antitumor antibiotics interfere with the DNA inside cells. This slows or stops cancer cells from growing and keeps them from multiplying. These agents are used to treat leukemias and certain types of cancer such as bladder cancer, and may be given either systemically or regionally.

About the Author
Dr. Hardeman is a board-certified oral and maxillofacial surgeon currently in his 25th year of practice. After spending 24 years in private practice in Orlando, Fla, he has transitioned into an academic position at the University of Florida (UF) College of Dentistry. He holds the position of clinical assistant professor of oral and maxillofacial surgery and is director of the predoctoral program of oral and maxillofacial surgery at the UF College of Dentistry. He graduated from the University of Missouri, Kansas City School of Dentistry, and the University of Illinois College of Medicine in Urbana, Ill. He completed a residency in oral and maxillofacial surgery at Carle Foundation Hospital and Clinics in Urbana. His clinical interests include dentoalveolar surgery, trauma, pathology and implants, and he has extensive experience in the areas of hard- and soft-tissue grafting for preparation of the oral cavity for future implant placement. Further areas of interest include team organization and preparation for office-based emergencies, and he has created several Web-based programs to facilitate the training of dental teams for unexpected emergencies. He can be reached at jhardeman@dental.ufl.edu.

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anthracycline medications in this group work on all phases of the cell cycle. Examples of this group of antitumor antibiotics agents include: Adriamycin, Danorubicin, Epirubucin, and Idarubicin. Drugs such as Mitomycin, Actinomycin-D, Bleomycin, and Mitoxantrone are types of antitumor antibiotics but are not in the anthracycline group.

**Topoisomerase Inhibitors**

These drugs interfere with a specific type of enzyme in the nucleus called *topoisomerases*. Topoisomerases help separate the strands of DNA so they can be copied during the S phase. Inhibitors of these enzymes prevent DNA replication and hence slow the propagation of the cancer cells. These chemotherapeutic agents are used to treat certain leukemias, as well as lung, ovarian, gastrointestinal, and other cancers. They are divided into 2 groups:

- Topoisomerase I inhibitors include Topotecan and Irinotecan.
- Topoisomerase II inhibitors include Etoposide, Teniposide, and Mitoxantrone (also acts as an antitumor antibiotic [see previous classification]). Topoisomerase II inhibitors can increase the risk of acute myelogenous leukemia, which may arise as a second cancer as early as 2 to 3 years after the drug is given.

**Mitotic Inhibitors**

Mitotic inhibitors are derived from plants and other compounds derived from natural products. They work by stopping mitosis in the M phase of the cell cycle, but can damage cells in all phases by keeping enzymes from making proteins needed for cell reproduction. Cancer cell types most often treated by these agents include breast and lung cancer, myelomas, lymphomas, and leukemias.

**Other Agents Used In Chemotherapy**

Multiple other medications are now being used in the cellular fight against malignancies (Table 1).

*Corticosteroids* are perhaps one of the most common agents used in combination with the other chemotherapeutic agents. Used in high doses, these steroids (dexamethasone in particular) function as adjuvants in cancer patients. Corticosteroids
Chemotherapy Agents and Dentistry

Chemotherapy may be used alone or as adjuvants in combination with other palliative or antineoplastic treatments. For example, corticosteroids may help prevent nausea, vomiting, and hypersensitivity reactions to treatment with chemotherapy or radiation. They are also commonly used as appetite stimulants in patients with advanced cancer. In the adjuvant setting, corticosteroids help to alleviate pain in advanced cancer patients, including specific situations such as back pain related to epidural compression.6

Biologic medications have now been developed to target specific cell types in cancers. Biological therapy involves the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Some biological therapies for cancer use vaccines or bacteria to stimulate the body’s immune system to act against cancer cells. These types of biological therapy, referred to collectively as “immunotherapy” or “biological response modifier therapy,” do not target cancer cells directly. Other biological therapies, such as antibodies or segments of genetic material (RNA or DNA), do target cancer cells directly. Biological therapies that interfere with specific molecules involved in tumor growth and progression are also referred to as targeted therapies.5

Monoclonal antibodies (MAbs) are laboratory-produced antibodies that bind to specific antigens expressed by cells, such as a protein that is present on the surface of cancer cells. These same antigens are not usually found on normal, healthy cells. Some MAbs stimulate an immune response that destroys cancer cells. Similar to the antibodies produced naturally by B cells, these MAbs “coat” the cancer cell surface, triggering its destruction by the immune system. Rituximab (Rituxin) was one of the first MAbs approved by the US Food and Drug Administration. It specifically targets the B-lymphocyte antigen CD20 found on non-Hodgkin’s lymphoma cells. Another group of MAbs stimulates an anticancer immune response by binding to receptors on the surface of immune cells and inhibiting signals that prevent immune cells from attacking the body’s own tissues, including cancer cells. Still other MAbs interfere with the action of proteins that are necessary for tumor growth.4

Cytokines are signaling proteins that are produced by white blood cells (WBCs). They help control immune responses, inflammation, and new blood cell formation. There are 2 main types of cytokines used to treat patients with cancer: interferons and interleukins. A third group, called hematopoietic growth factors, is used to counteract some of the side effects of certain chemotherapy regimens. They stimulate the formation of new blood cell lines in patients with suppressed bone marrow activity as a result of chemotherapeutic suppression.4

Table 1. Classification of Chemotherapy Medications

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Alkylating agents</td>
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<tr>
<td>Antimetabolites</td>
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<tr>
<td>Antitumor antibiotics</td>
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<tr>
<td>Topoisomerase inhibitors</td>
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Table 2. Classification of Chemotherapy Medications

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Additional Therapies

There are a host of other therapies that are still in the experimental phases of development but show promising hope of progress against malignant cell lines. These therapies include: cancer treatment vaccines, oncolytic virus therapy, adoptive T-cell transfer therapy, and gene therapy.

SIDE EFFECTS OF CHEMOTHERAPY AGENTS

Because chemotherapy agents affect the life cycles of dividing cells, it is important to understand that virtually all living and dividing cells can be affected. Side effects occur when normal cells in the body are also involved (Table 2). These will vary from person to person and depend on the type and location of cancer, the treatment dose, and the person’s overall health.5 Common side effects caused by chemotherapy drugs include fatigue, pain, oral mucosal lesions, diarrhea, constipation, nausea and vomiting, and blood dyscrasias. The nervous system may also be affected and both central and peripheral nerves may be involved with side effects.5 Patients may also develop problems with thinking and memory as a result of these medications. Sexual dysfunction, loss of appetite, and loss of hair are also commonly reported side effects. Most of the side effects are short-term, and these systems recover after the assault by these medications is over. However, there can be lingering effects that last for longer periods of time or may be permanent.5

As dental patients are treated with these drugs, clinicians need to be aware of the physical effects these treatments may cause. In a study published in the Journal of the American Dental Association, it was noted that “mucosal ulcerations, xerostomia, and bacterial and fungal infections were the most frequently encountered oral problems.”6

Patients undergoing cancer chemotherapy often suffer from oral complications as a result of their disease and its treatment. The effects of the chemotherapy on the bone marrow and oral mucosa, coupled with the patient’s immunosuppressed state and altered oral microbial flora, predispose these patients to oral mucositis, infection, and hemorrhage. Ulcers typically arise within 2 weeks after initiation of chemotherapy. Agents such as...
Chemotherapy Agents and Dentistry

the antimetabolites and alkylating agents cause a higher incidence and severity of oral mucositis. The lesions typically heal within approximately 2 to 4 weeks after the last dose of chemotherapy. The oral mucosa appears to mirror the effects of the chemotherapy on the bone marrow, as there appears to be a direct relationship between the changing peripheral blood counts and the status of the oral mucosa (Figures 1 to 3).7

In patients with severe neutropenia, a common side effect of chemotherapy treatment, ulceration of the oral mucosa (neutropenic ulcer) is frequently seen. Xerostomia secondary to treatment leads to rampant decay, which is often noted to affect the cemento-enamel junction region of the teeth. Low WBC levels in these patients often make them more susceptible to bacterial and fungal infections. The concomitant presence of breaks in the oral mucosa in an environment rich in microbiota has resulted in the well-reported relation between the mouth and bacteremias and sepsis among myelosuppressed patients.8

Bone marrow suppression as a result of chemotherapy can lead to blood disorders. These may be manifested as anemia, neutropenia, and thrombocytopenia. The clinical manifestations of these in dental patients include fatigue and the inability of patients to care for themselves and being less able to carry out routine dental hygiene regimens. The incidence of dental decay and periodontal issues is much higher in these patients. Neutropenia—low WBC counts—make patients much more susceptible to infections. These infections would otherwise be warded off by the patients’ natural immune system if they were healthy. Low platelet counts (thrombocytopenia) often lead to bleeding during and after invasive procedures. Therefore, it is imperative to know the patient’s platelet count prior to the initiation of any surgical or invasive procedure. Typically, platelet counts greater than 50,000 result in minimal bleeding. The normal range of platelet counts in a healthy individual is 150,000 to 350,000 per mL.9 The low point of blood cell counts in chemotherapy patients is known as the “nadir.” The body will continue to produce blood cells, and often the counts will rebound from the nadir in a period of 3 to 4 weeks. This effect of suppression and rebound of the blood counts is often taken into account when planning the cycle of chemotherapy.

Management of Dental Patients Undergoing Chemotherapy

Management of dental patients who are undergoing chemotherapy requires a complete understanding of their medical condition and pre-existing state of health prior to initiation of treatment. The effect of chemotherapy on a previously healthy patient is much different than on a patient who has already been affected by a compromised health issue. Age of the patients when initiating chemotherapy also has a great impact upon their overall reaction to the fight against cancer. Finally, there is also a psychological effect that must be recognized in patients, as this relates to their overall attitude regarding their recovery and oral maintenance.

Elimination of acute sources of infection must be a top priority of the dental provider. If it is known that the patient will begin chemotherapy, these areas of potential infection should be addressed prior to the start of the cancer therapy. These patients are being invaded by a myriad of drugs during their treatment, and many of these drugs directly affect the WBCs, the first line of defense against infections. Obvious decay should be eradicated. Dental abscesses or chronic infections should be treated in an efficacious and expeditious manner. Dental extractions, endodontic therapy, and acute phases of periodontal therapy should be initiated as soon as the patient presents to the office. These should not be treatment planned as long duration processes, because of the effects that chemotherapy will begin to take on their systems.

Maintenance therapy in the form of frequent recall and monitoring should be initiated in patients who have a pre-existing healthy dentition or those who have had their acute issues already addressed. Routine prophylaxis with scaling and root planing should be a staple in this stage of maintenance therapy. Consider the use of custom fluoride trays to help limit the degree of cervical caries, especially in patients who may also be receiving concomitant radiation therapy to the head and neck. All elective and cosmetic services should be delayed until the patients’ systems have recovered from the effects of the chemotherapy.

The primary focus in the management of cancer patients and those in whom myelosuppression is anticipated is clear-cut. The treatment of pre-existing infection and prevention and treatment of acute complications during medical therapy should be the mainstay of treatment. In neutropenic patients, the risk of infection during chemotherapy may require aggressive antimicrobial therapy. This can be a potentially life-threatening situation.10 Bacteremia due to oral sources has been well documented

<table>
<thead>
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<th>Table 2. Side Effects of Chemotherapy Medications</th>
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<tbody>
<tr>
<td>Fatigue</td>
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<tr>
<td>Pain</td>
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<td>Oral mucosal lesions: Ulcers, mucositis</td>
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<tr>
<td>Gastrointestinal tract: Diarrhea, constipation</td>
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<tr>
<td>Hair and skin: Loss of hair, thinning of nails, rash</td>
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<tr>
<td>Nausea and vomiting</td>
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<tr>
<td>Blood disorders: Low blood counts</td>
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<tr>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>Nervous system: Memory and mood changes, neuropathies</td>
</tr>
<tr>
<td>Psychological symptoms: Anxiety, depression</td>
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<tr>
<td>Other malignancies</td>
</tr>
</tbody>
</table>

7. The low point of blood cell counts in chemotherapy patients is known as the “nadir.”
8. Neutropenia—low WBC counts—make patients much more susceptible to infections.
9. The normal range of platelet counts in a healthy individual is 150,000 to 350,000 per mL.
10. Bacteremia due to oral sources has been well documented.
Chemotherapy Agents and Dentistry

in these immunosuppressed patients. The bacteria implicated include periodontal flora, streptococci, and staphylococci. More recently, an increase in streptococcal bacteremia has been reported in leukemic patients. The shift in the organisms identified in bacteremia may be due to improved antibacterial coverage of Gram-negative organisms, which are routinely included as part of the chemotherapeutic protocols. Systemic antibiotic prophylaxis may have an impact on exacerbation of preexisting periodontal disease.\(^\text{10}\)

Empiric antibiotic therapy for management of the febrile neutropenic patient is well established. The antibiotic must be broad spectrum, bacteriocidal, and given in appropriate dose and schedule. Guidelines for antibiotic therapy in neutropenic patients have been clearly established by the Infectious Diseases Society of America.\(^\text{11}\) For the nonallergic patient, broader spectrum penicillins such as Amoxicillin do well to target the infections caused by the oral flora. Amoxil 875 mg taken by mouth twice daily for 10 days is a very effective regimen. Because of the formulation and twice a day dosing, the compliance is usually much better. Metronidazole (Flagyl) appears to be an important antimicrobial in the management of oral infection associated with fever in neutropenic patients.\(^\text{10}\) It works through the creation of free radicals that disrupt the DNA strands in micro-organisms. The drug achieves high serum concentrations following oral administration and has excellent tissue penetration.\(^\text{12}\)

**SUMMARY**

During the course of a practice lifetime, nearly every dental practitioner will encounter one or more patients who have been stricken with cancer. There are a myriad of treatments currently available for the treatment of this disease, and this treatment commonly includes chemotherapy. Chemotherapy is the treatment of such disease processes by the use of chemical substances. These agents are now extremely sophisticated and very complex in their mechanism of actions and “targets” for which they are directed. This article reviewed the major classifications of chemotherapy agents, discussed the possible complications of their use, and reviewed management of these patients by the dental professional.♣

**References**

Chemotherapy Agents and Dentistry

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1. Chemotherapy drugs can be divided into several groups based upon:
   a. How they are formulated.
   b. Mechanism of action.
   c. Specific types of cell that they attack.
   d. All of the above.

2. Along with corticosteroids, there are how many main classes of chemotherapeutic agents?
   a. 2.
   b. 4.
   c. 5.
   d. 6.

3. Alkylating agents directly damage DNA to keep the cell from reproducing. These drugs work in all phases of the cell cycle.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

4. Mitomycin belongs to which class of chemotherapeutic drugs?
   a. Antimetabolites.
   b. Antitumor antibiotics.
   c. Topoisomerase inhibitors.
   d. Mitotic inhibitors.

5. Corticosteroids are perhaps one of the most common agents used in combination with other chemotherapeutic agents. They are commonly used as appetite stimulants in patients with advanced cancer.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

6. Interferons and interleukins are the 2 main types of:
   a. Corticosteroids.
   b. Mitotic inhibitors.
   c. Cytokines.
   d. None of the above.

7. The most common oral problem(s) associated with chemotherapeutic agents is/are:
   a. Mucosal ulcerations.
   b. Xerostomia.
   c. Bacterial/fungal infections.
   d. All of the above.
Chemotherapy Agents and Dentistry

8. Agents such as the antimetabolites and alkylating agents cause a higher incidence and severity of oral mucositis.
   a. True.
   b. False.

9. The normal range of platelet counts in a healthy individual is:
   a. 50,000 to 100,000 per mL.
   b. 100,000 to 150,000 per mL.
   c. 150,000 to 350,000 per mL.
   d. 350,000 to 500,000 per mL.

10. Low white blood cell count is known as:
    a. Neutropenia.
    b. Thrombocytopenia.
    c. Anemia.
    d. None of the above.
Chemotherapy Agents and Dentistry

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Please check the correct box for each question below.

1. □ [a]  □ [b]  □ [c]  □ [d]
2. □ [a]  □ [b]  □ [c]  □ [d]
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7. □ [a]  □ [b]  □ [c]  □ [d]
8. True  False
9. □ [a]  □ [b]  □ [c]  □ [d]
10. □ [a]  □ [b]  □ [c]  □ [d]

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