The anesthetic implications of chemotherapy

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In this article, the author discusses the history and current utilization of chemotherapeutic agents, emphasizing their mode of action and physiologic side effects. The interaction of these drugs with anesthetic agents and management is discussed in respect to the pre-, intra-, and post-operative periods.

The number of patients receiving chemotherapy as a treatment for cancer has steadily increased over the past three decades. Many of these patients are subjected to elective and emergency surgical procedures. The burgeoning number of agents available today has made it imperative that the anesthetist understand and appreciate the pharmacologic interaction of these agents with the current anesthetic armamentarium, as well as the physiologic alterations experienced by the patient as a result of these drugs.

Cancer chemotherapy in the United States dates back to the 18th century. In 1748, the House of Burgesses of the General Assembly of Virginia, with George Washington and James Madison as members, passed a resolution appointing a committee to make trial of Mary Johnson's "receipt [sic] of curing cancer," consisting of garden sorrel, celanidine, persimmon bark and spring water, and to report on its efficacy. Subsequently, after many witnesses had testified that the preparation had cured them of cancer, she was rewarded 100 pounds. Since that time, numerous agents have been reported to be effective anticancer drugs, with many passing the rigors of testing prior to release for human utilization. Scientific investigation, however, did not begin in earnest until the 1940s.

Sulfur mustard was the first alkylating agent scientifically studied for its cytotoxic effects. In 1942, nitrogen mustards were first used to treat cancer patients; however, they produced a multitude of side effects. In the course of investigating new compounds in the hopes of discovering one with minimal side effects, a profusion of cytotoxic agents has resulted, each with their own unique set of side effects.

Mechanism of action

The mechanism of action generic to cytotoxic agents is an alteration in DNA synthesis and/or function. The drugs act predominantly on the enzymes and substrates which are necessary for the synthesis of DNA as well as its appropriate functioning. Malignant tissues primarily consist of rapidly proliferating cells; therefore, these agents exert the majority of their action on this type of cell. However, many normal cells also have a high proliferative capacity, particularly bone marrow, gastrointestinal mucosa, skin and hair follicle cells. As a result, the side effects of these drugs are exemplified by symptoms characteristic of destruction of these cells—leukopenia, anemia, nausea, vomiting, dermatitides and alopecia.

The following discussion describes the char-
acteristics of each class of chemotherapeutic drug, as well as the pre-, intra- and post-operative considerations necessary for the successful anesthetic management of the patient being treated with these drugs.

**Antimetabolites**

Farber and associates in 1948 discovered that patients on folic acid therapy experienced a striking, although temporary, remission of their leukemia. The dramatic clinical results obtained by Farber in the treatment of acute leukemia in children ushered in the era of chemotherapy and specifically revealed the clinical utility of antimetabolites.\(^\text{1}\)

Currently, the folate analog of clinical importance is methotrexate. Other antimetabolite agents coming into widespread use include mercaptopurine, fluorouracil, and cytarabine. The major lesions associated with these drugs occur in the gastrointestinal tract and bone marrow. Buccal mucosal ulceration and stomatitis, as well as severe diarrhea resulting in hemorrhagic enteritis and possible intestinal perforation, may result from administration of these drugs.

**Alkylating agents**

The use of alkylating agents dates back to the interval between the World Wars, when extensive studies of the biological and chemical actions of

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### Table I

**Classification of chemotherapeutic agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Type of Agent/Drug</th>
<th>Nonproprietary Name</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Nitrogen mustards</td>
<td>Mechlorethamine</td>
<td>Hodgkins disease, breast, ovary</td>
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<td></td>
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<td>Busulfan</td>
<td>Chronic granulocytic leukemia, polycythemia vera</td>
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<td>Chlorambucil</td>
<td>Chronic lymphocytic leukemia, Hodgkins disease, breast, ovary</td>
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<td></td>
<td></td>
<td>Cyclophosphamide</td>
<td>Multiple myeloma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma</td>
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<td>Thiotepa</td>
<td>Retinoblastoma, breast, ovary</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Folic acid analogs</td>
<td>Methotrexate</td>
<td>Mycosis fungoides, Osteogenic sarcoma</td>
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<tr>
<td></td>
<td>Pyrimidine analogs</td>
<td>Fluorouracil</td>
<td>Breast, colon, stomach, pancreas, pre-malignant skin lesions</td>
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<td></td>
<td>Purine analogs</td>
<td>Cytarabine</td>
<td>Acute granulocytic and acute lymphocytic leukemia</td>
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<td></td>
<td>Azaribine</td>
<td>Polycythemia vera</td>
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<td></td>
<td></td>
<td>Mercaptopurine</td>
<td>Chronic granulocytic leukemia</td>
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<tr>
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<td>Thioguanine</td>
<td>Acute granulocytic and acute lymphocytic leukemia</td>
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<tr>
<td>Natural products</td>
<td>Vinca alkaloids</td>
<td>Vinblastine (VLB)</td>
<td>Hodgkins disease, breast, renal, testis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vincristine (VCR)</td>
<td>Acute lymphocytic leukemia, neuroblastoma, &quot;oat cell&quot;</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Dactinomycin</td>
<td>Daunorubicin</td>
<td>Choriocarcinoma, Wilms' tumor</td>
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<tr>
<td></td>
<td></td>
<td>Bleomycin</td>
<td>Acute granulocytic and acute lymphocytic leukemia</td>
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<td></td>
<td></td>
<td>Mitomycin C</td>
<td>Testis, head, neck, skin, esophagus, genitourinary tract</td>
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<tr>
<td></td>
<td></td>
<td>Mitomycin</td>
<td>Pancreas</td>
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<tr>
<td></td>
<td></td>
<td>Doxorubicin</td>
<td>Testis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Acute lymphocytic leukemia, breast</td>
</tr>
</tbody>
</table>
the nitrogen mustards were conducted. The original intent was to use these compounds in biological warfare. Research indicated, however, that there could be a more constructive use of these compounds. In 1942, nitrogen mustard was first used to treat cancer patients. The prevalent alkylating agents used today include mechlorethamine, busulfan, chlorambucil, cyclophosphamide, and thiopeta.

The mechanism of action of the alkylating agents is at the DNA binding sites and results in the inactivation of the molecule. The primary side effect is severe bone marrow depression. Thrombocytopenia and leukopenia accompany therapy and constitute the major limitation on the amount of drug that can be given in a single course. A rapid destruction of bulky tumor mass can produce an increased purine and pyrimidine breakdown, resulting in uric acid nephropathy. Pneumonitis and pulmonary fibrosis have also been reported as well as an inhibition of plasma cholinesterase resulting in prolonged paralysis following the administration of succinylcholine.

**Vinca alkaloids**

The therapeutic properties of the periwinkle plant, a species of myrtle, have been described in medicinal folklore for many years in various parts of the world. In experimental investigations which attempted to substantiate its hypoglycemic effect, Noble and associates in 1958 observed granulocytopenia and bone marrow suppression following the administration of a vinca alkaloid. This ultimately resulted in the use of vinca alkaloids as chemotherapeutic drugs for cancer.

Vincristine and vinblastine are the prototypes for this class of cancer drug. Their mechanism of action appears to be related to an inhibition of protein synthesis, resulting in mitotic arrest. Leukopenia is the most frequent side effect but neurologic toxicity may also occur in the form of paraesthesias, ataxia, foot drop, muscle wasting and loss of deep tendon reflexes. Toxicity of the autonomic nervous system may result in severe abdominal pain and constipation, with bowel obstruction and perforation as possible consequences.

**Antibiotics**

The antibiotics used for clinical purposes are natural by-products of certain soil fungi. These drugs act by forming relatively stable complexes with DNA, thereby inhibiting its synthesis. The antibiotic drugs used most frequently for chemotherapy are doxorubicin, daunorubicin, bleomycin, mithramycin and mitomycin C.

The cytotoxic effect of bleomycin is very similar to radiation therapy; some studies have suggested a synergistic action between the two modes of treatment. Dermatologic reactions are the most common side effects and include hyperpigmentation of pressure areas, inflammation of the hands and generalized erythema. These symptoms are seen in approximately 45% of the patients receiving bleomycin. Pulmonary toxicity is the primary dose limiting factor and is reported in 10-25% of patients.

At a histologic level, manifestations are comparable to those of diffuse interstitial pneumonitis and fibrosis. The lower lobes are more frequently involved, with the chest X-ray showing bilateral basilar and perihilar reticulonodular infiltrates with fibrosis. Cough, dyspnea and bibasilar rales are the first symptoms of toxicity. The clinical course and prognosis are very difficult to predict. Patients on bleomycin appear to be very susceptible to the adult respiratory distress syndrome (ARDS). A factor which is linked to this susceptibility is the concentration of inspired oxygen. Studies have indicated that bleomycin somehow sensitizes the lung to oxygen concentrations that are normally not detrimental. A maximum inspired concentration of 30% is recommended along with judicious use and careful monitoring of fluid replacement.

The anthracycline antibiotics, doxorubicin and daunorubicin, are highly toxic chemotherapeutic agents. In clinical usage, some 40% of this class of drug is metabolized, therefore, any compromise in liver function will increase the toxicity. Bone marrow depression and cardiac toxicity are the dose-limiting side effects. A dose related congestive heart failure (CHF) and nonspecific electrocardiographic (ECG) changes which occur during the course of therapy are the two major cardiac side effects.

The CHF induced by doxorubicin is heralded by a dry, nonproductive cough which rapidly progresses to congestive heart failure. Patients with existent ECG changes are at an increased risk of developing CHF secondary to doxorubicin administration. The pathological mechanism of action involves a loss of cardiac cells, resulting in cardiac depression with subsequent cardiac dilatation (which is refractory to cardiotoxic drugs). Elevated serum enzyme levels occur late in the clinical picture and are not useful as an early diagnostic tool. Once these symptoms develop, death can occur within three weeks.

ECG abnormalities have occurred in approximately 10% of the patients on doxorubicin therapy. The most common arrhythmias include:
supraventricular tachyarrhythmias, premature ventricular contractions, abnormalities of conduction and left axis deviation. These abnormalities occur during therapy at all dose levels, regardless of the schedules.

**Anesthetic management**

The multitude of side effects induced by the chemotherapeutic agents necessitates a thorough preoperative assessment and evaluation of the patient. The plan for anesthetic management should be designed to minimize stress on those physiological systems already taxed by the chemotherapeutic regimen. Prior to the selection of the anesthetic technique, the following laboratory data should be procured: CBC, U/A, serum electrolytes, fasting blood sugar, BUN, CO₂ content, platelet count, serum osmolality, liver function tests, creatinine, bilirubin, amylase, chest x-ray, ECG, and arterial blood gases (ABG).

Myelosuppression usually reverses itself within 1-6 weeks following termination of the chemotherapy. Anemia may be treated by transfusions of packed cells prior to surgery in conjunction with fresh frozen plasma to prevent intraoperative and postoperative coagulopathy. Patient antibodies may make crossmatching extremely difficult. A preoperative coagulation study may be indicated in patients on mechlorethamine and L-asparaginase therapy. The coagulation defect associated with these agents is not caused by a thrombocytopenia.

Immunosuppression occurs with all the chemotherapeutic agents and requires expediency and meticulous aseptic technique associated with the administration of anesthesia. Insertion of peripheral intravenous lines, arterial lines, central venous pressure (CVP) monitors, pulmonary artery catheters, endotracheal tubes and breathing circuits can function as the nidus for potentially lethal iatrogenic infections.

Cardiac toxicity requires extreme care and delicacy in the administration of anesthesia. Agents producing the least cardiac depression must be utilized in conjunction with prudent replacement of fluid and electrolyte losses. Operating and recovery room monitoring should include ECG, U/A, CVP, and when appropriate, arterial and pulmonary artery pressure monitors.

Dyspnea and exertional dyspnea must alert the anesthetist to the possibility of pneumonitis and pulmonary fibrosis secondary to bleomycin or methotrexate administration. Chest x-ray and ABGs may provide valuable baseline data, however, clinical findings appear to be more informative than pulmonary function tests concerning severity of the pathology. Patients on bleomycin therapy should not receive an inspired oxygen concentration greater than 30% and ventilatory support should be anticipated in the postoperative period. Fluid replacement should be carried out with colloids to further reduce the potential incidence of pulmonary edema.

Hepatotoxicity is also a major side effect of the chemotherapeutic agents and thus, necessitates the use of anesthetic agents with little or no metabolism. The availability of isoflurane has reduced the dilemma associated with volatile anesthetics and hepatic metabolism.

Central nervous system and autonomic nervous system toxicity results in peripheral neuropathies, particularly with vincristine administration. The utilization of conduction anesthesia needs to be carefully evaluated prior to its use in the patient who presents with neuropathies. A preoperative evaluation to include the sensorium and all neurologic deficits is necessary in order to appropriately assess any postoperative side effects that can be associated with the anesthetic management.

Thiotepa and cyclophosphamide produce significant reductions in anticholinesterase activity. The judicious use of succinylcholine and monitoring with a peripheral nerve stimulator will reduce the necessity for postoperative ventilation associated with prolonged apnea.

Diarrhea is a side effect of many of the agents. Careful examination of the fluid status of the patient preoperatively is imperative. Intraoperative measurement of urine osmolarity, specific gravity and serum electrolytes will provide adequate information in managing fluid problems associated with these patients.

**Summary**

There are numerous implications in managing the anesthesia for patients on chemotherapy. A thorough understanding of the mechanism of action and physiologic side effects of these agents will allow for a physiologically stable anesthetic course.

**REFERENCES**

AUTHOR

Salvatore Ciresi CRNA, MSN, is a graduate of the Frances Payne Bolton School of Nursing in Cleveland, Ohio. He completed the U.S. Army Nurse Anesthesia Course in 1977, and received his Master of Science in Nursing degree with a pulmonary specialty from the University of Washington in Seattle in 1980. Mr. Ciresi has spoken at numerous conferences including the AANA Annual Meeting in 1982. He also presented original research at the Annual American Thoracic Society meeting in May, 1981. He is presently an Assistant Professor and Director of Research and Clinical Projects in the Department of Nurse Anesthesia, Medical College of Virginia, in Richmond, Virginia.