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CHEMOCOCKTAILS: WHEN & HOW TO USE THEM, A GUIDE TO CHEMOTHERAPY

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INTRODUCTION
It is imperative that veterinary technicians involved in administering antineoplastic agents have a working knowledge of their mechanism of action, administration, metabolism, and toxicities.

BACKGROUND
The life cycle of normal and tumor cells consist of several phases. The M phase (mitosis) is the period of actual cell division, the G1 phase is the 1st “gap” (post-mitotic or pre-synthetic), the S phase is the period of DNA synthesis, the G2 phase is the 2nd “gap” (pre-mitotic or post-synthetic), and cells in a resting state are in a G0 phase. These cells can be entered in the mitotic cycle. Antineoplastic agents that act at a specific phase of the cell cycle are called cell-cycle or cycle-phase specific. Those that act independently of a phase are called cell-cycle or cycle-phase nonspecific. Combining drugs that target different phases of the tumor cell cycle provides the best utilization of the killing potential of the particular drugs.

DRUG CLASSIFICATIONS
Chemotherapy drugs are classified as alkylating agents, antimetabolites, antitumor antibiotics, plant alkaloids (or mitotic inhibitors), hormones, and miscellaneous neoplastic agents

ALKYLATING AGENTS
Alkylating agents cross-link DNA, which prevents the cell from dividing. Because they are active during several phases of the cell cycle, alkylating agents are considered cell cycle phase-nonspecific.

Alkylating agents are more effective if they are administered on an intermittent basis at high doses than a lower dose given daily. The alkylating agents commonly used in veterinary medicine include:

Cyclophosphamide (Cytoxan®): available in 200 mg, 500 mg, 1g or 2 g vials for injection and 25 mg or 50 mg oral tablets. Injectable cyclophosphamide is reconstituted with sterile water for injection. 0.9% saline or bacteriostatic water for injection. The manufacturers recommendation is to store them in the refrigerator and use within 6 days.

Reconstituted vials of cyclophosphamide should be well shaken and allowed to sit for 10-15 minutes prior to IV administration to ensure the drug is completely dissolved.
The kidneys excrete cyclophosphamide and its metabolites. Patients with renal compromise may need to be treated at lower doses. The liver is necessary to activate cyclophosphamide, so patients with liver disease may also require dose adjustments.

Toxicities involved with the use of cyclophosphamide include vomiting (especially with IV administration, which should be done over a 20-30 minute period). Using the oral form may reduce this.

Leukopenia usually occurs during the nadir period, which is 7-10 days after administration. The recovery period is 7-10 days after the nadir period. Complete blood counts should be checked during the nadir period to determine if a dose reduction is necessary.

The metabolites of cyclophosphamide have been shown to be irritating to the bladder wall resulting in hemorrhagic cystitis. Administering cyclophosphamide orally, in the morning, along with the addition of diuretics (furosemide), frequent urination, and increased fluid intake can be helpful in preventing hemorrhagic cystitis. If cyclophosphamide induced hemorrhagic cystitis does occur, then the drug must be discontinued and chlorambucil may be substituted.

Cyclophosphamide is most commonly used in the treatment of lymphoma, leukemias, soft tissue sarcomas (combined with vincristine and doxorubicin), feline mammary neoplasia (combined with doxorubicin), and other sarcomas.

The dose of cyclophosphamide is typically 250 mg/m² PO every 3 weeks or 50 mg/m² PO daily 3-4 days/week.

Chlorambucil (Leukeran®): available in 2 mg oral tablets, which require refrigeration and are light sensitive. Chlorambucil is absorbed almost completely by the GI tract. Reports indicate that the metabolites of chlorambucil are excreted by the kidneys but its metabolism is not completely understood.

Toxicities associated with chlorambucil include bone marrow suppression, alopecia, and gastrointestinal signs (vomiting and diarrhea).

Chlorambucil is used for the treatment of lymphoma (especially in patients with cyclophosphamide induced hemorrhagic cystitis) and chronic lymphocytic leukemia as well as various immune mediated diseases.

The dose of chlorambucil is 20 mg/m² PO every 2-3 weeks, 2 mg PO every 2-3x weekly, 0.1 mg/kg PO daily or 6-8 mg/m² PO daily.

Melphalan (Alkeran®): available in 2 mg oral tablets or 500 mg vials for injection. Melphalan requires refrigeration and the injectable form must be used within 60 minutes of reconstitution.

Absorption of the oral form is through the GI tract but is variable and is eliminated by hydrolysis in the plasma.

Toxicities with the use of melphalan are usually associated with marked myelosuppression, which can take up to 4 weeks to recover from. Gastrointestinal signs are infrequently seen.

Melphalan has been most commonly used to treat multiple myeloma. Combining with vincristine, prednisone or cyclophosphamide may enhance remission times.

The induction dose of melphalan is 2-4 mg/m² PO daily for 7 days then 2-4 mg/m² every 48 hours as a maintenance dose or 0.1 mg/kg PO daily for 10 days the 0.05 mg/kg PO daily as a maintenance dose.

Cisplatin (Platinol®): available in 10 mg, 50 mg, or 100 mg vials for injection. The dry powder form is stable at room temperature for 2 years and the reconstituted solution is stable at room temperature for 20 hours. Cisplatin is light sensitive and refrigeration may cause precipitate to form.

Cisplatin can be administered via intravenous, intracavity, or intrasional routes. Aluminum needles should be avoided because aluminum may displace platinum from the cisplatin molecule resulting in the formation of a black precipitate. Discard if precipitate is present.

Cisplatin is distributed very quickly into the liver, kidney and intestines but has poor penetration into the central nervous system. The concentration of cisplatin is less than 10% in the plasma after 1 hour. Approximately 50% of cisplatin is...
excreted in the patient’s urine within 24-48 hours of the drug administration.

Kidney function tests should be evaluated prior to each treatment due to the nephrotoxic nature of cisplatin. Patients with above normal serum creatinine levels should have a dose reduction and small dogs are more at risk of developing nephrotoxicity than large dogs.

Pretreatment diuresis with 0.9% saline for 4 hours prior to cisplatin administration at a rate of 20-25 mls/kg/hr is critical to maintain proper hydration and to avoid the nephrotoxic side effects of the drug. After cisplatin administration, continue the post diuresis with 0.9% saline for 2 hours.

Nausea and vomiting (may be severe) are common side effects associated with cisplatin and can be seen as soon as 1 hour post administration. Studies have shown that treating with butorphanol at a rate of 0.4 mg/kg IM one-half hour prior to or just after cisplatin administration may help prevent gastric side effects.

Cisplatin had a bimodal nadir period and myelosuppression (moderate to severe) may be seen in 7 and 14 days.

Cisplatin is contraindicated in cats due to the possibility of fatal pulmonary edema.

The dose of cisplatin is 50-70 mg/m² IV every 3 weeks for 4 treatments (can be used in conjunction with doxorubicin for osteosarcoma).

Cisplatin is most commonly used in the treatment of osteosarcoma, squamous cell carcinoma, bladder tumors, ovarian carcinoma, and mesotheliomas.

**Carboplatin** (Paraplatin®): available in 50 mg, 150 mg, and 450 mg vials for injection. Reconstitute with 5% dextrose in water (using 0.9% saline may cause a toxic cisplatin-like drug). The dry powder form is stable for 2 years at room temperature. Carboplatin is stable for 8 hours at room temperature if reconstituted.

Carboplatin is similar to cisplatin in that it is metabolized by the liver and kidney but doesn’t have the same gastric or renal toxicities of cisplatin. Bone marrow suppression, specifically thrombocytopenia, is the most significant side effect associated with carboplatin use.

Use of carboplatin is similar to that of cisplatin however, carboplatin can be safely used in cats.

The dose of carboplatin is 300 mg/m² in dogs under 0.7 m² and 350 mg/m² in dogs over 0.7 m². In cats, the dose of carboplatin is 175 mg-210 mg/m².

**Lomustine** (CeeNu®, CCNU): available in 10 mg, 40 mg or 100 mg oral capsules. Store at room temperature.

Lomustine is metabolized in the liver and excreted in urine. Patients with decreased renal or hepatic function should be monitored closely.

Myelosuppression (particularly thrombocytopenia) may be moderate to severe. If platelet counts drop below 100,000/mcl, discontinuation of the drug is advised until thrombocytopenia resolves. Lomustine has a bimodal nadir period (day 7 and day 21) after treatment has been initiated (1 week the most common). CBC’s should be monitored prior to each treatment.

Lomustine is an effective chemotherapy agent in the treatment of lymphoma, mast cell disease, CNS neoplasms, and other tumor types.

The dose of lomustine is 60-90 mg/m² every 3-4 weeks in the dog and a single 10 mg capsule in the cat every 3-4 weeks. Treatment times may be delayed further if laboratory values are abnormal.

**ANTITUMOR ANTIBIOTICS**

Antitumor antibiotics prevent DNA and RNA synthesis and are cell cycle phase nonspecific. The most common antitumor antibiotic used in veterinary medicine is doxorubicin.

**Doxorubicin** (Adriamycin®): available in 10 mg, 20 mg, 50 mg 150 mg and 200 mg vials for injection. A powder form is available and is reconstituted with 0.9% saline. The powder form is stored at room temperature and is stable for several months after reconstitution. The liquid form is stored in the refrigerator and is stable for 18 months. Doxorubicin is light sensitive.

Doxorubicin is a potent tissue irritant. Extravasation of the drug may result in tissue sloughing.

Infuse with 0.9% saline prior to (to assure catheter patency) and immediately after (to prevent extravasation of any remaining drug) doxorubicin administration. Avoid using with heparinized saline and aluminum needles as a precipitate may form.

Doxorubicin is metabolized by the liver and is rapidly distributed in plasma and tissues. Only about 5% of doxorubicin is excreted in the urine. Owners should be warned that after treatment with doxorubicin, the patient’s urine might be red-tinged from the drug not from hemorrhage.

Toxicities associated with doxorubicin include myelosuppression (especially neutropenia and thrombocytopenia), hemorrhagic colitis (usually 2-4 days after administration), allergic reactions (urticaria, pruritis, anaphylaxis), alopecia, and cardiotoxicity (not to exceed cumulative dose more than 180-240 mg/m² without cardiac evaluation-echocardiogram is the most definitive).

Doxorubicin is used as a single agent or in combination with other antineoplastic drugs in the treatment of lymphoma, soft-tissue sarcomas, hemangiosarcoma, thyroid carcinoma, and mammary adenocarcinoma.

The dose of doxorubicin is 15-30 mg/m² in dogs and in cats and small dogs (10 lbs and under); the dose is 1 mg/kg every 3 weeks.

**PLANT ALKALOIDS**

Plant alkaloids are extracted from the periwinkle plant (*vinca rosea*). Plant alkaloids are active during the M phase by disrupting the mitotic spindle, so they are cell cycle phase-specific. Vincristine, and vinblastine are the two plant alkaloids used in veterinary oncology.

**Vincristine** (Oncovin®): available in 1 mg/1 ml, 2 mg/2 ml, or 5 mg/5 ml vials for injection. Store in the refrigerator.

Vincristine is rapidly cleared from serum and is excreted in the bile. Patients with bilirubin levels > 2 mg/dl should have their dose reduced by 50%.

Administration of vincristine is with a butterfly or indwelling catheter as a bolus injection. Follow injection with a thorough saline flush (10cc). Vincristine is a potent tissue irritant that may cause phlebitis and necrosis. Extravasation may result in tissue sloughing.

Toxicities associated with vincristine include gastrointestinal (constipation, bloating, paralytic ileus, anorexia), and neurological (paresthesia). Bone marrow suppression is rarely a problem unless vincristine is given in combination with L-asparaginase (Elspar®)

Vincristine is used in the treatment of lymphoma, transmissible venereal tumors (TVT’s) and mast cell tumors.

The dose of vincristine is 0.5 mg-0.75 mg/m² weekly or as an adjuvant drug in a specific protocol.
**Veterinary Technician**

**Vinblastine (Velban®):** available in 10 mg (1 mg/ml) vial for injection, in powder or liquid form. Store reconstituted solution in the refrigerator. Once reconstituted, it is stable for 30 days.

Vinblastine is similar to vincristine in metabolism and excretion. Unlike vincristine, vinblastine may cause severe myelosuppression. The nadir period is 4-7 days post administration and CBC’s should be closely monitored.

Administration of vinblastine should be through a butterfly or indwelling catheter to prevent extravasation. Follow injection with a thorough saline flush (10cc). Vinblastine is also a potent tissue irritant.

Vinblastine has shown to be successful in the treatment of mast cell disease and lymphoma.

The dose of vinblastine is 2 mg/m² every 3 weeks in combination with adjuvant chemotherapy drugs. It is rarely used as a single agent.

**HORMONES**

Corticosteroids are the most common hormones used to treat cancer in animals and do not result in the same potential adverse side effects seen with other hormones. Hormones interfere with the cellular receptors that stimulate cell division and growth. Prednisone is the drug of choice in the hormone classification. Injectable forms can be used if difficulty pilling, and are effective for shorter time periods.

**Prednisone:** available in 5 mg, 10 mg, 20 mg, and 50 mg tablets; 1 mg/ml syrup; 2 mg/ml injectable (dexamethasone), 4 mg/ml injectable (dexamethasone sodium phosphate), 2 mg/ml injectable (Vetalog); other dosage forms are also available. Store at room temperature. Some forms of prednisone may be light sensitive.

Metabolism of prednisone is via the liver and it is excreted in the urine.

Polyphagia, polydipsia, polyuria, and tachypnea are associated with the use of prednisone. Alopecia, hind end weakness, softened ligaments, and other symptoms of iatrogenic Cushing’s disease can be associated with long-term prednisone use.

Prednisone does not provide a sustainable remission when used as a single agent for lymphoma. However, it is effective as a single agent treatment for mast cell disease.

The dose of prednisone is variable. Dosages higher than 40 mg/m² may result in gastric ulceration. Refer to treatment protocols for desired dosage.

**MISCELLANEOUS AGENTS**

Miscellaneous agents are drugs whose mechanisms are not completely understood or differ from the agents that have been previously identified. Enzymes are the most common miscellaneous agents used in chemotherapy.

**L-Asparaginase (Elspar®):** available in 10,000 unit vials for injection. Store lyophilized vials in the refrigerator. Reconstitute with 0.9% saline or sterile water for injection. According to the manufacturer, any unused portion should be discarded after 8 hours. However, other sources report that unused portions may be refrigerated for up to 14 days without losing efficacy.

Metabolism of L-Asparaginase is not completely understood.

Toxicities with L-Asparaginase include allergic and anaphylactic reaction (pretreatment with antihistamines and steroids may reduce reactions), fever, vomiting, and acute pancreatitis has been documented with L-Asparaginase.

L-Asparaginase is used as an adjuvant agent for lymphoma and lymphoblastic leukemia. Single agent treatment does not provide sustainable remissions.

The dose of L-Asparaginase is 10,000 units/m² IM or SQ, however, repeated dosing increases the risk of anaphylaxis.

**References** available from author upon request.