Commonly Used Chemotherapy Drugs
Part 1

This 2-part article will discuss 9 anticancer chemotherapy drugs commonly used in dogs and cats.
- **Part 1** will include carboplatin, chlorambucil, cyclophosphamide, and doxorubicin.
- **Part 2** will include L-asparaginase, lomustine (CCNU), mitoxantrone, vincristine, and vinblastine.

See the Table (page 66) for a brief overview of all 9 drugs.

**CARBOPLATIN**
Indications & Advantages
- Carboplatin, a cisplatin analog, has a broad spectrum of anticancer activity against carcinomas and sarcomas (notably, osteosarcomas in dogs).
- Carboplatin is rarely emetogenic, does not cause renal toxicity in dogs, and is tolerated at normal dosages in cats. Therefore, it has largely replaced cisplatin, which is nephrotoxic in dogs and causes death in cats, in clinical veterinary practice.

Safe Administration
- Carboplatin can usually be administered every 3 weeks in dogs and every 4 weeks in cats. However, it is eliminated primarily through renal excretion, and even subclinical alterations in renal function can alter excretion and lead to prolonged and occasionally severe myelosuppression. This is particularly true in older cats; they may need a dosage interval of 6 or more weeks before another dose can be administered safely.
- Careful evaluation of complete blood count, serum biochemical profile, and urine specific gravity is recommended before determining the dose to use.
- Carboplatin can be given to patients with renal disease, but dosages need to be adjusted and renal values monitored closely, particularly if using in conjunction with other...
potentially nephrotoxic drugs, such as nonsteroidal antiinflammatory drugs.

- In humans, dosing is determined by analyzing renal function test results rather than by body weight; when available, renal function (creatinine clearance) tests also allow more accurate dosing for dogs and cats.

**Disadvantages & Contraindications**
- Acute toxicities are rarely recognized with chlorambucil administration; however, in pets receiving the drug long-term, monitoring is warranted.
- Myelosuppression is the most common toxicity and is usually associated with long-term administration. Blood counts should be initially monitored every 2 weeks; then every 8 to 12 weeks for prolonged use.
- Liver toxicity is not commonly reported, but seizures in cats receiving pulse high-dose chlorambucil have been reported, and I have documented further patients with this effect.

**CYCLOPHOSPHAMIDE**

**Indications & Advantages**
- Cyclophosphamide is efficacious in treatment of lymphoma in both dogs and cats, and has some activity in treatment of soft-tissue sarcomas and some carcinomas.
- It is available in intravenous and oral (50-mg tablets, and 25-mg tablets in the U.S.) formulations.
- Metronomic cyclophosphamide therapy is low-dose daily administration of the oral formulation; this protocol has been shown to reduce the risk of recurrence of soft-tissue sarcomas.

**Safe Administration**
- Many veterinary oncologists prefer intravenous cyclophosphamide. Intravenous administration allows accurate administration of the ideal dose, particularly in smaller pets, and makes it easier to predict toxicity.
- Oral cyclophosphamide administration typically results in inaccurate dosing. In addition, it is not completely absorbed, requiring a higher oral dose to achieve the same bioavailability as the intravenous dose.
- The exception to the above is metronomic administration.
administration, in which a low oral dose (10 mg/m²) is delivered using reformulated capsules.

- Cyclophosphamide is a prodrug that requires hepatic activation; administration to a patient with functional hepatopathy may result in inadequate levels of active drug.

Disadvantages & Contraindications
- Myelosuppression (primarily neutropenia) is the most common acute toxicity and occurs at a predictable time; blood counts should be evaluated 7 days after first dose and 7 days after any dose adjustment.

- In older literature, the incidence of hemorrhagic cystitis was relatively high (around 20%) and most common after multiple doses. The practice of administering a single dose of furosemide after cyclophosphamide administration (and after flushing the catheter) has reduced incidence to a negligible level.
- Sterile hemorrhagic cystitis is a diagnosis of exclusion, and bacterial cystitis is an important differential. Dogs that develop sterile hemorrhagic cystitis should be treated with aggressive supportive care, and cyclophosphamide should not be administered again.

DOXORUBICIN

Indications & Advantages
- Doxorubicin is the most active agent against canine lymphoma and has activity against sarcomas—notably, osteosarcomas in dogs, hemangiosarcoma, and soft-tissue sarcomas in both dogs and cats.
- Doxorubicin also has efficacy against carcinomas, such as mammary carcinoma.

Safe Administration
- Doxorubicin is given intravenously with an over-the-needle catheter. While different administration techniques have been suggested, our preferred method is to administer undiluted drug into the injection port of a running saline infusion over 10 to 20 minutes or at a rate of approximately 1 mL undiluted drug per minute, whichever is slower.
- Rapid infusion may be associated with histamine release and anaphylactoid reaction (restlessness, urticaria, vomiting, collapse); slow infusion avoids this complication.
- Some administration techniques suggest concurrent administration of antihistamines and corticosteroids to reduce the risk of allergic reaction. I have found this strategy unnecessary, but there is no harm in doing so.
- Normal saline is recommended for flushing because heparin may cause precipitate to form.

Disadvantages & Contraindications

Extravasation
- Doxorubicin is a powerful vesicant when given perivascularly; only clean “first-stick” catheters should be used, and catheters being used for intravenous fluid administration should not be used.
- If accidental extravasation occurs, intravenous administration of dexrazoxane should be considered:
  - Give dexrazoxane at 10 x the mg dose of doxorubicin within 3 hours
  - Or give 400 to 600 mg/m² of dexrazoxane intravenously over 15 minutes.
  - The selected dexrazoxane dose should be repeated 24 and 48 hours after extravasation.
- This treatment has a high likelihood of preventing severe tissue necrosis but should be accompanied by ice-packing (to patient’s tolerance).
- Under no circumstances should the area be flooded with saline as this will further disperse the doxorubicin and enlarge the extravasation reaction.

Myelosuppression
- Myelosuppression (primarily neutropenia) is the most common acute toxicity and occurs at a predictable time; blood counts should be evaluated 7 days after first dose and 7 days after any dose adjustment.
- Prophylactic trimethoprim-sulphamethoxazole, which has been shown to reduce risk of hospitalization and gastrointestinal side effects in dogs treated with doxorubicin, is recommended.

CONTINUES
Gastrointestinal Toxicity
- Gastrointestinal toxicity is seen in up to 30% of patients; in most, toxicity is mild and self-limiting.
- Vomiting is not usually a significant problem for most dogs; however, metoclopramide given for 4 to 5 days following each doxorubicin dose will reduce risk of nausea. I usually dispense the medication so owners can start it at their discretion at the first sign of nausea. As with pain, nausea is easier to prevent than to treat.
- For severe vomiting or dogs at excessive risk, maropitant (subcutaneously or orally once daily) or serotonin antagonists, such as dolasetron or ondansetron, can be given with great effect. Significant vomiting is not considered an acceptable side effect and should warrant future dose reduction.
- Colitis may occur and is occasionally associated with rectal bleeding. Prophylactic measures, such as high-fiber diet and, potentially, metronidazole therapy, may reduce risk and severity of gastrointestinal effects and allow continued treatment without dose reduction.

Cardiotoxicity
- Cumulative doxorubicin cardiotoxicity, which is progressive even after therapy is ceased, is a major disadvantage of doxorubicin administration.
- In normal dogs, the total cumulative dosage of doxorubicin should be restricted to a maximum of 180 mg/m², which is approximately 6 treatments; some veterinary oncologists are more conservative.
- My advice is to avoid doxorubicin therapy in dogs with cardiac abnormalities when an alternative effective drug exists (eg, mitomycin or carbo-platin in dogs with lymphoma and carboplatin in dogs with osteosarcoma); if there is any doubt regarding the significance of a cardiac abnormality, consultation with a veterinary cardiologist should be recommended.
- In breeds predisposed to developing dilated cardiomyopathy, risk of cardiac toxicity appears to be high if doxorubicin is given. In one study of over 300 dogs treated with doxorubicin, nearly half the Dobermans and
Great Danes developed clinical cardiomyopathy despite normal pretreatment echocardiography. While it is not possible to judge whether this rate is higher than for dogs of the same breeds not treated with doxorubicin, availability of alternative chemotherapy drugs with similar efficacy implies that doxorubicin should not be the first choice for these breeds.

Renal & Hepatic Toxicity
- Doxorubicin is a renal toxin in cats; consequently, cats should be carefully evaluated for renal disease before administering each dose of doxorubicin.
- In cats with preexisting renal disease, doxorubicin should not be administered.
- Doxorubicin should be used with caution in patients with hepatic dysfunction.

In summary, the administration of chemotherapeutic drugs to veterinary patients should be undertaken only after evaluation for other intercurrent diseases that could alter drug elimination and full consideration of the patient’s sensitivities. The therapeutic margin is very narrow for these drugs, and toxicity can be fatal. Although not addressed in this review, chemotherapy should never be given without considering the safety of staff, pet owners, and handlers.

See Aids & Resources, back page, for references and suggested reading.
### An Overview of Commonly Used Chemotherapy Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effective Against</th>
<th>Administration</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Carboplatin</td>
<td>• Carcinoma&lt;br&gt;• Sarcoma (most notably osteosarcoma in dogs)</td>
<td>• IV&lt;br&gt;• Q 3 wks in dogs; Q 4 wks in cats&lt;br&gt;• Longer interval may be needed in older cats</td>
<td>• Myelosuppression&lt;br&gt;• GI toxicity uncommon in cats &amp; large dogs; more likely in small dogs</td>
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<tr>
<td>Chlorambucil</td>
<td>• Chronic lymphoid leukemia (dogs)&lt;br&gt;• Low-grade lymphoma (particularly GI in cats)</td>
<td>• Oral&lt;br&gt;• Low daily or alternate day dosage&lt;br&gt;• Or higher &quot;pulse&quot; dosage Q 3–4 wks</td>
<td>• Acute toxicities rare (seizures documented with pulse dose)&lt;br&gt;• Myelosuppression associated with tumors in long-term administration&lt;br&gt;• Liver toxicity uncommon but documented</td>
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<tr>
<td>Cyclophosphamide</td>
<td>• Lymphoma (dogs &amp; cats)&lt;br&gt;• Soft-tissue sarcoma&lt;br&gt;• Some carcinomas</td>
<td>• IV accurate &amp; easier to predict toxicity&lt;br&gt;• Oral inaccurate &amp; not completely absorbed&lt;br&gt;• Metronomic administration is effective oral method (low dose of reformulated capsules)</td>
<td>• Myelosuppression most common acute toxicity&lt;br&gt;• Risk of hemorrhagic cystitis reduced by single dose of furosemide after cyclophosphamide administration</td>
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<tr>
<td>Doxorubicin</td>
<td>• Lymphoma (dogs)&lt;br&gt;• Sarcoma&lt;br&gt;• Osteosarcoma (dogs)&lt;br&gt;• Hemangiosarcoma&lt;br&gt;• Soft-tissue sarcoma (dogs &amp; cats)</td>
<td>• IV with over-the-needle catheter&lt;br&gt;• Rapid infusion associated with anaphylactoid reaction&lt;br&gt;• Normal saline recommended for flushing instead of heparin</td>
<td>• Extravasation&lt;br&gt;• Myelosuppression&lt;br&gt;• GI toxicity&lt;br&gt;• Cardiotoxicity&lt;br&gt;• Renu toxicity (cats)</td>
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<tr>
<td>L-asparaginase</td>
<td>• Lymphoma (very effective in dogs but less so in cats)</td>
<td>• SC or IM&lt;br&gt;• Reconstitute slowly&lt;br&gt;• Preadministration of antihistamines recommended by some oncologists</td>
<td>• Anaphylactic reaction&lt;br&gt;• Vomiting &amp; urticaria&lt;br&gt;• Myelosuppression in some patients if administered with vincristine</td>
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<tr>
<td>Lomustine (CCNU)</td>
<td>• Lymphoma (dogs &amp; cats)&lt;br&gt;• Mast cell tumors (dogs &amp; cats)&lt;br&gt;• Histiocytic sarcoma&lt;br&gt;• Some brain tumors</td>
<td>• Highly absorbed orally&lt;br&gt;• Available in 10-, 40-, and 100-mg capsules but can be reformulated to smaller sizes for cats and small dogs</td>
<td>• Neutropenia&lt;br&gt;• Cumulative thrombocytopenia&lt;br&gt;• Hepatotoxicity&lt;br&gt;• Nephrotoxicity &amp; pulmonary fibrosis uncommon</td>
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<tr>
<td>Mitoxantrone</td>
<td>• Lymphoma (dogs)&lt;br&gt;• Some carcinomas (dogs)&lt;br&gt;• Less effective in cats</td>
<td>• IV with over-the-needle catheter&lt;br&gt;• Normal saline is recommended for flushing instead of heparin</td>
<td>• Myelosuppression (primarily neutropenia)&lt;br&gt;• Colitis (can be severe &amp; hemorrhagic)</td>
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<tr>
<td>Vincristine</td>
<td>• Lymphoma (dogs &amp; cats)&lt;br&gt;• Venereal tumors (dogs)&lt;br&gt;• Soft-tissue sarcoma (in combination protocols)</td>
<td>• Only IV&lt;br&gt;• Can be delivered as bolus injection of undiluted drug</td>
<td>• Potentially myelosuppressive when administered with L-asparaginase&lt;br&gt;• Anorexia in some dogs &amp; cats&lt;br&gt;• Neurotoxicity (rare)</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>• Mast cell tumors (dogs)&lt;br&gt;• Potentially lymphoma (dogs &amp; cats)</td>
<td>• Only IV&lt;br&gt;• Can be delivered as bolus injection of undiluted drug</td>
<td>• Myelosuppression (primarily neutropenia)</td>
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*GI = gastrointestinal; IM = intramuscular; IV = intravenous; SC = subcutaneous*

*This table can be downloaded and printed for use in your clinic at cliniciansbrief.com.*