Which Drugs Are Used for Medical Management of Lymphoma in Dogs & Cats?

Part 1 of a 3-Part Series

Christine Mullin, VMD, DACVIM (Oncology)
Craig A. Clifford, DVM, MS, DACVIM (Oncology)
Hope Veterinary Specialists
Malvern, Pennsylvania

The following drugs can be used in the management of lymphoma in dogs and cats. Part 1 will discuss asparaginase, doxorubicin, vincristine, cyclophosphamide, and lomustine.

- Asparaginase
- Doxorubicin
- Vincristine
- Cyclophosphamide
- Lomustine
- Chlorambucil
- Corticosteroids (prednisone and derivatives)
- Cytarabine
- Mechlorethamine
- Procarbazine
- Dacarbazine
- Actinomycin D
- Melphalan
- Mitoxantrone

Asparaginase

Asparaginase, also known as L-asparaginase, is a bacteria-derived enzyme used in both the naïve and relapse setttings for dogs and cats with intermediate- to high-grade lymphoma, most commonly as part of multiagent chemotherapy protocols.[1-6]

Mechanism of action → Depletes the pool of asparagine, an amino acid required for protein synthesis and cell division

- Although normal cells can replenish their own pool of asparagine, malignant lymphocytes lack ability to synthesize it; depletion of asparagine can interrupt the cell cycle, leading to apoptosis.[1,2]

COMMON CHEMOTHERAPY PROTOCOLS

- CHOP = cyclophosphamide, [(3)H] daunorubicin/doxorubicin, vincristine (Oncovin), prednisone
- COP = cyclophosphamide, vincristine (Oncovin), prednisone
- DMAC = dexamethasone, melphalan, actinomycin, cytarabine
- MOPP = mechlorethamine, vincristine (Oncovin), procarbazine, prednisone
- MPP = mechlorethamine, procarbazine, prednisone

Dose (dogs, cats) → 400 units/kg or 10 000 units/m^2 SC or IM once (can be repeated at relapse)[3]

Monitoring during therapy → Serial CBC evaluations, hepatobiliary parameters, renal function

- Asparaginase does not typically cause myelosuppression on its own, but because it is often given with other cytotoxic chemotherapeutics (eg, vincristine; see ***Key Points***), CBC evaluations should be frequently performed.

Adverse Events

- Hypersensitivity reactions are uncommon with first-time administration but can occur with subsequent doses.
  - Clinical signs include pruritus, urticaria, facial swelling, restlessness, and, in rare cases, vomiting, diarrhea, and collapse.[1-3]
  - In patients with mild anaphylactic reactions, administration of a steroid (ie, dexamethasone sodium phosphate 0.1-0.2 mg/kg IV) often minimizes the effects.
    - For subsequent doses, administration of an antihistamine (eg, diphenhydramine 2 mg/kg in dogs, 1 mg/kg in cats) SC 20 to 30 minutes before asparaginase is indicated.
- Protein synthesis abnormalities are possible but are rare and poorly characterized in veterinary patients.
- Pancreatitis, hepatotoxicity, coagulation dyscrasias, and delayed wound healing are possible.[1,2]

Key Points

- Asparaginase requires reconstitution, and data suggest that it remains viable after a freeze–thaw cycle.[7]
  - Aliquots for subsequent doses can be made for individual patients (especially useful in cats).[7]
- When administered concurrently with vincristine, neutropenia is noted in up to 40% of dogs at day 7 postadministration.[8]
  - Using a lower vincristine dose or delaying vincristine administration by a few days may help prevent myelosuppression.[8]
- In patients with large tumor burdens, hepatic disease, renal disease, or dehydration, vigilant monitoring and pre-emptive supportive care for possible acute tumor lysis syndrome are indicated.[9]
- Decreased efficacy develops after repeated administration and may be partially linked to development of antibodies, which can reduce enzyme activity.[1,2]
- Two retrospective studies noted no significant difference in overall response rates, duration of remission, or survival rate when asparaginase was excluded from a CHOP-based protocol[4,5]; however, the ability of asparaginase to rapidly improve patient quality of life on therapy initiation makes it valuable for many patients.
- One study that prospectively evaluated the effect of asparaginase in cats with lymphoma showed only a 30% objective response rate.[10]

Doxorubicin

Doxorubicin, an antitumor antibiotic in the anthracycline drug class, is most often used to treat canine and feline intermediate- to high-grade lymphoma as a single agent or as part of CHOP-based protocols.[2,3,11-15]

Mechanism of action → Has several anticancer mechanisms of action, including DNA intercalation, inhibition of DNA and RNA polymerases, inhibition of topoisomerase II, alkylation of DNA, production of free oxygen radicals, and alterations in cellular calcium homeostasis, among others[2,3,11]

- These various actions ultimately can lead to halted DNA and RNA synthesis, DNA strand breakage, and cell death.[2,3,11]

Dose (dogs) → Weighing <15 kg, 1 mg/kg IV; weighing >15 kg, 30 mg/m^2 IV,[3] in week 4 of each cycle of CHOP protocol or q3wk when used as single agent

Dose (cats) → 1 mg/kg IV[3] during week 4 of each cycle of CHOP protocol or q3wk when given as single agent[13,14,16,17]

Monitoring during therapy → Serial CBC evaluations, hepatobiliary parameters, renal function

Adverse Events

- Hypersensitivity reactions are uncommon, are generally immediate in nature, and may be associated with speed of administration.
  - Anecdotally, may be more common in cats as compared with dogs
- Dose-dependent cumulative cardiotoxicity may occur in dogs.[2,3,11]
  - Risk for cardiotoxicity is believed to be increased in predisposed breeds (eg, Doberman pinscher, Great Dane, rottweiler, boxer) when the cumulative dose exceeds 180 to 240 mg/m^2.[2,3,11]
  - Arrhythmias, including tachycardia, may be noted, especially during rapid administration.[2,3,11]
- Nephrotoxicity has been reported in cats, although the

incidence and pathophysiology are poorly characterized.
  - Risk may increase if cumulative doses >100 mg/m^2 are reached.[3,16]
- GI signs (eg, anorexia, nausea, vomiting, diarrhea) may develop, particularly in the first 5 days following administration.[2,3,11]
- If perivascular extravasation develops, severe tissue damage may cause local pain, discomfort, regional tissue damage, and even extensive tissue necrosis.[2,3,11,18]
  - Doxorubicin-induced tissue sloughing usually appears 7 to 14 days after extravasation and progressively worsens over the next 2 to 3 months.[2,3,11,18]

Key Points
- Dilute in saline and deliver as slow infusion over 20 to 30 minutes.
  - Proper catheter placement is essential, and vigilant observation during administration is warranted to ensure proper delivery.
  - **Not recommended**: Dilution into fluid bag and/or use of infusion pumps
- Eliminated through hepatobiliary system[2,3,11]
  - Hepatobiliary disease can lead to delayed drug metabolism and increased risk for side effects.[2,3,11]
  - Dose reductions are indicated based on bilirubin and bile acid test results.[2,3,11]
- Mutation in the multidrug-resistance *MDR1* gene can lead to increased risk for severe side effects.[3,18]
  - Various breeds can be affected, including herding breeds, the silken windhound, and the long-haired whippet.[19]
  - Perform *MDR1* testing.[19]
    - If mutation (heterozygous) is present, major dose reduction is indicated; if patient is homozygous mutant, consider drug omission or substitution.[3,18]
- Some oncologists premedicate patients with a steroid (eg, dexamethasone sodium phosphate 0.1-0.2 mg/kg IV) and/or antihistamine (eg, diphenhydramine 2 mg/kg SC in dogs, 1 mg/kg SC in cats) 20 to 30 minutes before administration.[2,3,11]
- Clinicians often premedicate with an antinausea agent before doxorubicin administration.[20]
- Dexrazoxane can also be used as a cardioprotectant; however, no data exist regarding when the drug should be administered.[21]
  - Doxorubicin appears to be the most effective single agent for canine lymphoma, achieving high response rate and prolonged remission duration.[15,17,22]
  - For canine lymphoma, reported response rate was significantly higher in 1 study of dogs with B-cell immunophenotype (>86%), as compared with dogs with T-cell phenotype (50%).[22]
  - Prophylactic medications commonly used to prevent and/or decrease severity of adverse events include[23]:
    - Maropitant: 1 mg/kg SC or IV or 2 mg/kg PO q24h for 5 days
    - Ondansetron: 0.2-0.5 mg/kg PO q8-24h
    - Metoclopramide: 0.2-0.5 mg/kg PO q8-24h
    - Metronidazole: 7.5-15 mg/kg PO q12h
  - Dexrazoxane therapy is indicated if extravasation occurs.
    - Adminstered within 3 hours of extravasation then repeated at 24 and 48 hours
    - Administered as an IV infusion in a different vein at 10× the doxorubicin dose[24]

CHOP = cyclophosphamide, [(3)H] daunorubicin/doxorubicin, vincristine (Oncovin), prednisone

COP = cyclophosphamide, vincristine (Oncovin), prednisone

MOPP = mechlorethamine, vincristine (Oncovin), procarbazine, prednisone

Vincristine

Vincristine, a naturally occurring vinca alkaloid derived from the periwinkle plant, is most commonly used to treat both canine and feline lymphoma as part of first-line COP- or CHOP-based protocols but can also be used in multiagent rescue protocols.[2,3,12-14,25-28]

Mechanism of action → Binds to distinct site on tubulin proteins to inhibit tubulin polymerization and thus microtubule assembly, which can lead to disruption of the mitotic spindle, metaphase arrest, and subsequent cell death[2,25]

Dose (dogs, cats) → 0.5-0.75 mg/m^2 IV once a week on weeks 1 and 3 of each cycle as part of CHOP protocol, once a week on weeks 1 through 4 of each cycle of COP protocol, once a week on weeks 1 and 2 of each cycle of MOPP protocol[3,27,28]

Monitoring during therapy → Serial CBC evaluations, hepatobiliary parameters

Adverse Events
- Myelosuppresion (primarily neutropenia at day 7 post-administration)[2,3,25]

- GI upset, especially ileus and subsequent constipation in cats (attributed to autonomic neuropathy within intestines)[2,3,25]
- Peripheral neuropathy secondary to damage associated with axonal microtubules (typically occurs with chronic administration)[2,3,25]
- Mild-to-moderate tissue damage (if perivascular extravasation present)[2,3,25]

Key Points

- Because vincristine is eliminated through the hepatobiliary system, hepatobiliary disease can lead to delayed drug metabolism and increased risk for side effects.[2,3,25]
  - Dose reductions are based on bilirubin and bile acid test results.[2,3,25]
- Mutation in the multidrug-resistance *MDR1* gene can lead to increased risk for severe side effects.[3,18]
  - Numerous breeds are affected, including various herding breeds, the silken windhound, and the long-haired whippet.[19]
  - Perform *MDR1* testing.[19]
    - If mutation (heterozygous) is present, major dose reduction is indicated; if patient is homozygous mutant, consider drug omission or substitution.[3,18]
- Vincristine and its sister drug vinblastine are composed of the same chemical structure, differing only in a substitution on the central rings.[2,25]
- Vinblastine can be substituted for vincristine in patients with higher risk for ileus or peripheral neuropathy, as vinblastine has lower affinity for axonal tubules.[25]
  - Decreased GI upset and comparable efficacy have been shown in cats that have lymphoma and are undergoing multiagent chemotherapy with vinblastine instead of vincristine.[26]
    - Similar data do not exist in dogs, but vinblastine substitution can be made if indicated (eg, history of GI upset, neurologic disease).
  - Myelosuppression (primarily neutropenia at day 7 postadministration) associated with vinblastine tends to be more significant than what occurs with vincristine.[25]

Cyclophosphamide

Cyclophosphamide, an alkylating agent of the nitrogen mustard family, is most commonly used as part of COP- and CHOP-based protocols in treatment of both canine and feline intermediate- to high-grade lymphoma. The drug is also used as a rescue agent in cats with small cell GI lymphoma.[2,3,12-14,29,30]

Mechanism of action → Active metabolites covalently bind alkyl groups to DNA to form bifunctional adducts that generate interstrand and/or intrastrand breaks, leading to disruption of DNA synthesis and subsequent cell death.[2,29]

Dose (dogs, cats with intermediate- to high-grade lymphoma) → 200-250 mg/m^2 IV bolus (dogs, cats) or PO over 1-4 days (dogs), given on week 2 of each cycle of CHOP protocol or on weeks 1 through 4 of each cycle of COP protocol[3,12]

Dose (cats with small cell GI lymphoma, second-line protocol) → 200-250 mg/m^2 divided and administered on days 1 and 3 every other week[30]

Monitoring during therapy → Serial CBC evaluations, urinalysis if concern for sterile hemorrhagic cystitis

Adverse Events

- Myelosuppression (primarily neutropenia at day 7 postadministration)[2,3,29]
- GI upset[2,3,29]
- Sterile hemorrhagic cystitis attributed to direct irritation of bladder mucosa from active metabolite acrolein[3,29,31]
- Hair loss (more common in dogs with continually growing coats)[29]

Key Points

- Similar exposure to active metabolite is achieved between oral and IV administration.[3]
- As a prodrug, cyclophosphamide must undergo metabolic activation by hepatic mixed-function oxidases into the active alkylating intermediate phosphoramide mustard.[29]
  - Hepatic insufficiency can decrease metabolic activation and thus drug efficacy.[29]
- A response rate of 100% has been reported in cats receiving cyclophosphamide as second-line treatment of small cell GI lymphoma.[30]
- In dogs, risk for sterile hemorrhagic cystitis significantly decreased when oral doses were split over 3 days rather than given 1 day or with concurrent administration of furosemide and IV cyclophosphamide.[32]
- Increased risk for urinary bladder cancer has been reported in humans receiving this agent; however, to date this risk is anecdotal in dogs.[29]

Lomustine

Lomustine, also known as CCNU, is a nitrosourea alkylating agent most commonly used as a single agent, although it can also be administered in combination or as part of a multiagent protocol for relapsed or resistant canine and feline lymphoma. More recently, lomustine has been used as part of first-line protocols for canine T-cell lymphoma. The drug may also have a role in rescue settings for both canine and feline low-grade lymphoma or chronic lymphocytic leukemia.[3,6,33-35]

Mechanism of action → Generates active metabolites that bind alkyl groups directly to DNA, leading to intrastrand crosslinks and DNA-protein crosslinks, DNA strand breakage, disruption of DNA synthesis, and subsequent cell death[2,29]

Dose (dogs, when used as single agent) → 60-90 mg/mg^2 PO q3wk[3,36,37]; starting dose is dependent on size of dog (a smaller dog requires a lower starting dose), comfort level with agent, and clinician experience

Dose (cats, when used as single agent) → 40-60 mg/m^2 PO q3-6wk[3,38]

Monitoring during therapy → Serial CBC evaluations, hepatic enzymes, renal values

Adverse Events

- Myelosuppression can be severe and prolonged.[2,3,29,36]
  - In dogs, neutropenia occurs between 7 and 10 days postadministration.
  - In cats, neutropenia can occur anywhere between 7 and 28 days postadministration.
  - Thrombocytopenia typically occurs between 10 and 21 days postadministration.
- Hepatic damage and dysfunction are associated with repeated administration.[3,29,36,39,40]
  - Coadministration of CCNU and drugs containing *S*-adenosylmethionine and silybin (eg, Denamarin; nutramaxlabs.com) is associated with reduced frequency of grade IV hepatotoxicity, as Denamarin increases glutathione levels and provides antioxidant properties.[41]
- GI upset uncommon, typically mild[3,29,36]
- Pulmonary fibrosis reported in humans[29]
  - Anecdotally in cats[42]
- Secondary cancer formation in humans[29]
  - Anecdotally/theoretically in veterinary patients

CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea

CHOP = cyclophosphamide, [(3)H] daunorubicin/doxorubicin, vincristine, prednisone

Key Point

- Crosses blood–brain barrier and thus has a role in treating CNS lymphoma[2,3,29]

See references at **plumbstherapeuticsbrief.com**

CHRISTINE MULLIN, VMD, DACVIM (Oncology), is a medical oncologist at Hope Veterinary Specialists in Malvern, Pennsylvania. After earning her VMD, she completed a 1-year internship in small animal medicine and surgery at Red Bank Veterinary Hospital in New Jersey and a 3-year residency in medical oncology at The Oncology Service in the Washington, DC, metro area. Dr. Mullin serves on the Northeast Veterinary Cooperative Oncology Group committee and recently delivered a continuing education webinar course on chemotherapy in veterinary medicine. She has authored and coauthored multiple journal articles and book chapters on topics in veterinary oncology. Dr. Mullin received the Most Outstanding Resident Basic Science Research award at the annual Veterinary Cancer Society meeting in 2014.

CRAIG A. CLIFFORD, DVM, MS, DACVIM (Oncology), is the director of clinical studies at Hope Veterinary Specialists in Malvern, Pennsylvania, where he also serves as a medical oncologist and director of clinical studies. Dr. Clifford earned his DVM from Mississippi State University and his MS in animal science/virology from University of Delaware, then completed an internship and a medical oncology residency at University of Pennsylvania. He has authored and coauthored more than 50 papers and book chapters. Dr. Clifford created the Veterinary Cancer Society's resident review session and the Northeast Veterinary Cooperative Oncology Group and has served on the VCS executive board, ACVIM Examination Rating Committee, Residency Training and Credentials Committee, Oncology Pathology Working Group, Standards of Excellence in Residency Education Task Force, and Australian Scientist's Oncology Specialty Examination. Dr. Clifford also serves on the Scientific Advisory Boards for Industry.