

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

Part 2 of a 3-Part Series

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The following drugs can be used in the management of lymphoma in dogs and cats. Part 2 will discuss chlorambucil, corticosteroids (prednisone and derivatives), cytarabine, mechlorethamine, and procarbazine.

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

Chlorambucil

Chlorambucil, an alkylating agent of the nitrogen mustard family, is most commonly used to treat indolent, small cell, low-grade GI

lymphoma in cats; indolent, low-grade peripheral nodal lymphoma in dogs; and chronic lymphocytic leukemia in both dogs and cats. In addition, this drug is sometimes used as a substitute for cyclophosphamide in high-dose multiagent canine lymphoma protocols if patients have developed sterile hemorrhagic cystitis.¹⁻⁵

Mechanism of action → Binds alkyl groups directly to specific sites on DNA, which leads to interstrand and intrastrand cross-links, DNA strand breakage, disruption of DNA synthesis, and subsequent cell death¹⁻³

Dose (dogs with indolent lymphoma) → 6 mg/m² PO q24h for 10-14 days, then 3 mg/m² PO q24h or q48h as maintenance²

Dose (dogs with intermediate- to high-grade lymphoma, as substitute for cyclophosphamide when sterile hemorrhagic cystitis precludes additional cyclophosphamide doses) → 1.4 mg/kg PO once in place of cyclophosphamide in multiagent protocols^{2,6}

Dose (cats) → 2 mg PO q48h or 20 mg/m² PO q2-3wk^{4,5}

Monitoring during therapy → Serial CBC evaluations

Adverse Events

- ▶ Myelosuppression, primarily thrombocytopenia, can be cumulative and irreversible, attributable to cytotoxicity against slowly and/or noncycling hematopoietic stem cells. It may occur acutely (10-14 days postadministration) with high-dose protocols or over several months with low-dose chronic protocols.³
- ▶ GI upset typically very mild^{1,3-5}
- ▶ Rarely, myoclonus has been reported as a side effect of chlorambucil use in cats.⁷

Key Point

- ▶ A very high (>95%) response rate has been reported in cats treated with chlorambucil and steroids for small cell GI lymphoma.^{4,5}

Corticosteroids (Prednisone & Derivatives)

Prednisone, along with its derivatives prednisolone and methylprednisolone, is a catabolic steroid used as part of most chemotherapy protocols in both dogs and cats with lymphoma but carries some efficacy as a single agent against lymphocytes.^{2,4-6,8-16}

Mechanism of action → Binds to specific cytoplasmic receptors on cancer lymphocytes, enters the nucleus, and alters DNA synthesis, which leads to apoptosis²

Corticosteroids also reduce bone resorption of calcium, reduce intestinal calcium absorption, and increase renal calcium excretion; therefore, they are useful in patients with lymphoma-associated hypercalcemia.¹⁷

Dose (dogs, as single agent in lieu of chemotherapy) → 1-2 mg/kg PO q24h continuously^{2,18}

Dose (dogs, as part of chemotherapy protocol) → 2 mg/kg or 40 mg/m² PO starting dose, then tapered off over 4-6 weeks^{2,18}

Dose (cats with indolent, small cell, low-grade GI lymphoma) → 1-2 mg/kg q24h continuously⁴

Monitoring during therapy → Routine CBC evaluations, serum chemistry profile, urinalysis

Adverse Events¹⁸

- ▶ Short-term use
 - Polyuria/polydipsia
 - Polyphagia
 - Panting, restlessness (dogs)
 - GI ulceration with high doses
- ▶ Chronic use
 - Iatrogenic hyperadrenocorticism
 - Adrenal gland atrophy and iatrogenic hypoadrenocorticism after drug withdrawal
 - Iatrogenic diabetes mellitus (cats)
 - Exacerbation of underlying renal disease
 - Exacerbation of underlying cardiac disease, fluid overload (cats)
 - Proteinuria secondary to glomerular changes (dogs)
 - Muscle atrophy
 - Alopecia (dogs)
 - GI ulceration with high doses

Key Points

- ▶ In cats, oral prednisolone is believed to be more bioavailable than its prodrug prednisone.¹⁸
- ▶ In dogs, corticosteroid use may induce partial remission.¹⁹
 - Steroid use can also induce multidrug resistance when used as a single agent.¹⁹
 - Thus, rapid initiation of definitive therapy is paramount in dogs.²⁰
 - However, this has not been demonstrated in cats.²⁰
- ▶ Data suggest that inclusion of prednisone does not impact the overall efficacy of a multiagent protocol for lymphoma in dogs.²¹
 - However, it is helpful in clinically improving systemically ill patients and may have a palliative role in patients with malignant hypercalcemia.¹¹

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

Cytarabine

Cytarabine, also known as cytosine arabinoside and ara-C, is an antimetabolite agent most commonly used as part of multiagent protocols for relapse or resistant intermediate- to high-grade lymphoma in dogs and cats. The drug can be used as part of first-line protocols for patients with known CNS involvement or as part of the multiagent DMAC (dexamethasone, melphalan, actinomycin D, cytarabine) rescue protocol or if bone marrow involvement is documented.^{1,2,22,23}

Mechanism of action → As a pyrimidine (specifically cytidine) analog, cytarabine functions by competing with true pyrimidines for incorporation into an elongated DNA strand, thus leading to stalled DNA synthesis and subsequent cell death.²²

- ▶ Secondary mechanism of action: binding to DNA polymerase and acting as a competitive inhibitor, thus halting DNA synthesis and repair, subsequently leading to cell death²²

Dose (dogs, cats) → 150-300 mg/m² IV via CRI over 4-24 hours; 150 mg/m² IV or SC q24h for 5 consecutive days; or 400-600 mg/m² SC divided into 4 doses q12h over 2 days²²⁻²⁵

Based on cytarabine's mechanism of action and cell-cycle-specific nature, administration over the longest time frame is ideal; however, no prospective study comparisons of dose regimens have been performed in veterinary medicine.

Monitoring during therapy → Serial CBC evaluations

Adverse Events

- ▶ Myelosuppression^{1,2,22,23}
- ▶ Neutropenia and thrombocytopenia typically occur 7 to 10 days postadministration. The degree of neutropenia or thrombocytopenia likely correlates with the dose regimen and is thus more likely to manifest when the drug is administered as a constant-rate infusion over a prolonged time.
- ▶ GI upset^{1,2,22}

Key Points

- ▶ Crosses blood-brain barrier and thus has a role in treating CNS lymphoma^{1,2,22}
- ▶ Constant-rate infusion (but not SC administration) has been

shown to achieve steady-state concentrations, thus providing higher chance of therapeutic drug concentrations crossing into the CNS when constant-rate infusion vs intermittent SC administration is used.^{22,24}

- ▶ In addition to use in patients with known CNS involvement, cytarabine is commonly used in cats with renal lymphoma (40%-60% chance of spread to CNS with this form).¹¹
- ▶ Higher complete response rate and significantly prolonged survival were documented in dogs receiving cytarabine as part of a multiagent chemotherapy protocol for lymphoma with bone marrow involvement (as compared with similarly affected dogs receiving the same protocol without cytarabine).²⁵

Mechlorethamine

Mechlorethamine, an alkylating agent of the nitrogen mustard family, is most often used as part of the multiagent MOPP (mechlorethamine, vincristine [Oncovin], procarbazine, prednisone) protocol in the rescue setting of dogs and cats with intermediate- to high-grade lymphoma. The drug has also been evaluated as a first-line agent for treating T-cell and hypercalcemic lymphoma in dogs.^{1-3,13,14}

Mechanism of action → Breaks down into highly reactive, positively charged intermediates that bind alkyl groups directly to specific DNA sites. This can lead to interstrand and intrastrand crosslinks, DNA strand breakage, disruption of DNA synthesis, and subsequent cell death.³

Dose (dogs, cats) → 3 mg/m² IV

Note: This dose is in combination with other agents that make up the MOPP protocol and is generally administered on days 0 and 7 of the q3wk protocol.^{3,13}

Monitoring during therapy → Serial CBC evaluations

Adverse Events

- ▶ Myelosuppression¹⁻³
 - Neutropenia typically occurs around 7 days postadministration.
- ▶ GI upset¹⁻³
- ▶ Because of the potential for nausea, prophylactic antiemetics are typically given with this drug.
- ▶ Moderate-to-severe tissue damage if perivascular extravasation develops^{1,3}

DMAC = dexamethasone, melphalan, actinomycin D, cytarabine

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

Procarbazine has been evaluated as a first-line agent in the treatment of T-cell and hypercalcemic lymphoma in dogs.^{1,2,13,14,26}

Key Points

- ▶ When given as a first-line protocol for T-cell or hypercalcemic canine lymphoma, the MOPP protocol was associated with long-term survival (25% survival at >900 days).¹³

Procarbazine

Procarbazine is a methylating agent (alkylator) most commonly used as part of the multiagent MOPP protocol in the rescue setting for dogs and cats with intermediate- to high-grade lymphoma. The drug has also been evaluated as a first-line agent in the treatment of T-cell and hypercalcemic lymphoma in dogs.^{1,2,13,14,26}

Mechanism of action → Active metabolites bind methyl groups to specific DNA sites, which can lead to DNA strand breaks, inhibition of DNA/RNA/protein synthesis, and subsequent cell death.²⁶

Dose (dogs, cats) → 50 mg/m² PO q24h, typically for 7-14 days²⁷

Monitoring during therapy → Serial CBC evaluations

Adverse Events

- ▶ Myelosuppression^{1,2,26}
- ▶ Because of the dose schedule and this drug's almost exclusive use in combination protocols, it is difficult to know exactly how much of the myelosuppression seen in these patients is attributable to procarbazine.
- ▶ GI upset^{1,2,26}

Key Points

- ▶ Oral bioavailability of 100%²⁶
- ▶ Procarbazine is a prodrug that is bioactivated to active metabolites²⁶ by both enzymatic and nonenzymatic pathways.
- ▶ Dose adjustments are indicated in patients with hepatic dysfunction.
- ▶ Crosses the blood-brain barrier and thus has a role in treatment of CNS lymphoma^{1,2,26}

See references at plumbstherapeuticsbrief.com

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