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

## Part 3 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 3 will discuss dacarbazine, actinomycin D, melphalan, and mitoxantrone.

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

### Dacarbazine

Dacarbazine, a methylating agent (alkylator) also known as DTIC, is most often used as a single agent or as part of a combination chemotherapy protocol (eg, doxorubicin+DTIC, CCNU [lomustine] +DTIC, temozolomide+DTIC) in the rescue setting for dogs with intermediate- to high-grade lymphoma.[1-7]

***Mechanism of action*** → The exact mechanism underlying the antitumor activity of dacarbazine remains unknown.[4]

- However, it is thought that the active metabolites bind methyl groups to specific DNA sites, which leads to DNA strand breaks, inhibition of DNA synthesis, and subsequent cell death.[4]

***Dose (dogs only, as single agent)*** → 800-1000 mg/m$^2$ IV as slow infusion over 6 to 8 hours[5]

***Dose (dogs only, in combination with CCNU or anthracycline)*** → 600 mg/m$^2$ IV via similar infusion protocol[7]

- Frequency and duration can vary, depending on whether the drug is used as a single agent (q3wk) or as part of a multiagent protocol.[5,6]

CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
DTIC = 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide

***Monitoring during therapy*** → Serial CBC evaluations, assessment of hepatic function

**Adverse Events**

- GI upset, specifically acute emesis during infusion[1,2,4]
  - Injectable antiemetics recommended before infusion[1,2,4]
- Myelosuppression, particularly thrombocytopenia[1,2,4-6]
  - Neutropenia typically occurs 7 to 10 days postadministration.
  - Thrombocytopenia typically occurs between 10 and 21 days postadministration.
- Rare but severe hepatotoxicity reported in humans; unclear whether clinically significant in dogs[4]
- Hypotension can occur if the IV dose is administered rapidly.[4]
- Moderate-to-severe vesicant; extravasation injury can be severe.[8]

**Key Points**

- Dacarbazine is a prodrug that requires bioactivation to active metabolites.[4]
- Dose adjustments are indicated in patients with hepatic dysfunction.
- Has not been effectively evaluated in cats
  - Unknown whether cats can metabolize parent drug into active metabolites

## Actinomycin D

Actinomycin D, also known as dactinomycin, is an antitumor antibiotic of the mitomycin class of chemotherapy agents (ie, derivatives of the soil bacteria of the *Streptomyces* genus). This drug is most commonly used as a single agent or part of the multiagent rescue DMAC protocol for canine lymphoma.[1,2,9-13]

***Mechanism of action*** → Binds DNA at the transcription initiation complex and prevents RNA chain elongation by RNA polymerase, which leads to inhibition of RNA transcription or protein synthesis and altered cell metabolism[1,10]

***Dose (dogs only)*** → 0.5-0.7 mg/m$^2$ IV slowly over 15 to 20 minutes

- Frequency and duration can vary, depending on whether the drug is used as a single agent (q3wk) or incorporated in a multidrug protocol (eg, CHOP, DMAC).[9,11-13]

***Monitoring during therapy*** → Serial CBC evaluations

**Adverse Events**

- Myelosuppression, including neutropenia 7 to 10 days postadministration and thrombocytopenia ≥14 days postadministration[1,2,10,13]
- GI upset[1,2,10,13]
- Tissue damage if perivascular extravasation occurs[10]

**Key Points**

- First antibiotic shown to have anticancer activity[10]
- Mutation in the multidrug resistance *MDR1* gene (also known as *ABCB1-1Δ*) can lead to increased risk for severe side effects.[14]
  - Numerous breeds are affected with the *MDR1* mutation, including various herding breeds, the silken windhound, and the long-haired whippet.[14]
  - Perform *MDR1* testing.[15]
  - If mutation (heterozygous) is present, major dose reduction is indicated; if patient is homozygous mutant, consider drug omission or substitution.[2,14]
- DMAC protocol has not been evaluated in cats, but anecdotal experience suggests it is well-tolerated.
- Although actinomycin D is less cardiotoxic than doxorubicin, a randomized controlled trial of doxorubicin vs actinomycin D in a multiagent protocol for canine lymphoma documented decreased efficacy of a actinomycin D-based protocol.[11]
- Another study evaluated actinomycin D as part of maintenance therapy following a standard CHOP protocol for canine lymphoma and documented a higher complete response rate (97%) as compared with historical control studies.[12]

## COMMON CHEMOTHERAPY PROTOCOLS

- CHOP = cyclophosphamide, 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

## Melphalan

Melphalan, an alkylating agent of the nitrogen mustard family, is most commonly used to treat canine lymphoma as part of the multiagent DMAC rescue protocol.[1,2,9,16]

***Mechanism of action*** → Binds alkyl groups directly to specific DNA sites, which leads to interstrand and intrastrand cross-links, DNA strand breakage, disruption of DNA synthesis, and subsequent cell death[16]

***Dose (dogs only, for DMAC protocol)*** → 20 mg/m$^2$ PO on day 7 of a 14-day cycle of the DMAC protocol

***Monitoring during therapy*** → Serial CBC evaluations, assessment of renal function

### Adverse Events

- Myelosuppression, particularly thrombocytopenia[16]
  - Neutrophil nadir typically occurs around 7 to 10 days postadministration.
  - Platelet nadir can occur between 10 and 21 days post-administration.
  - Thrombocytopenia can be cumulative and irreversible because of cytotoxicity against slowly cycling and/or noncycling hematopoietic stem cells.[16]
- Increased toxicity seen with renal insufficiency[1,16]

### Key Points

- Active drug that does not require metabolic activation[16]

## Mitoxantrone

Mitoxantrone is a synthetic anthracenedione compound most commonly used as a rescue agent for intermediate- to high-grade canine lymphoma or as a substitute for doxorubicin in multiagent protocols.[1,2,17-19]

**Mitoxantrone causes less free-radical formation and oxidative damage as compared with doxorubicin.**

***Mechanism of action*** → Has multiple anticancer mechanisms of action, including DNA intercalation, inhibition of DNA and RNA polymerases, and inhibition of type II topoisomerase[17]

- These various actions ultimately lead to halted DNA and RNA synthesis, DNA strand breakage, and cell death.[17]

***Dose (dogs only)*** → 5-6 mg/m$^2$ IV q3wk (slow bolus)

- Many clinicians start at low end of dose range and escalate if the drug is well-tolerated.

***Monitoring during therapy*** → Serial CBC evaluations

### Adverse Events

- Myelosuppression[17,19]
  - Neutropenia and, to a lesser degree, thrombocytopenia typically occur between 7 and 10 days postadministration.[20]
- GI upset, typically mild[17,19]

### Key Points

- Causes less free-radical formation and oxidative damage as compared with doxorubicin and thus is not associated with cardiac toxicity in dogs[2,17]
  - Therefore, mitoxantrone can be used as a substitute for doxorubicin in dogs with cardiac disease and possible doxorubicin-induced cardiotoxicity.[2,17,21]
- Not associated with renal toxicity, so can be used as a substitute for doxorubicin in patients with significant renal disease[17]
- One study evaluated mitoxantrone as part of maintenance therapy following a standard CHOP protocol for canine lymphoma and documented longer remission and survival times as compared with historical controls.[18]

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

DMAC = dexamethasone, melphalan, actinomycin, cytarabine

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