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 methylation 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/m² IV as slow infusion over 6 to 8 hours⁵

**Dose (dogs only, in combination with CCNU or anthracycline)** → 600 mg/m² IV via similar infusion protocol⁷

- 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
  - Injectable antiemetics recommended before infusion
  - Neutropenia typically occurs 7 to 10 days postadministration.
  - Thrombocytopenia typically occurs between 10 and 21 days postadministration.
- Myelosuppression, particularly thrombocytopenia
  - 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
- Hypotension can occur if the IV dose is administered rapidly.
- Moderate-to-severe vesicant; extravasation injury can be severe.

**Key Points**
- Dacarbazine is a prodrug that requires bioactivation to active metabolites.
- 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.

**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.

**Dose (dogs only)** → 0.5-0.7 mg/m² 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)

**Monitoring during therapy** → Serial CBC evaluations

**Adverse Events**
- Myelosuppression, including neutropenia 7 to 10 days postadministration and thrombocytopenia ≥14 days postadministration
- GI upset
- Tissue damage if perivascular extravasation occurs

**Key Points**
- First antibiotic shown to have anticancer activity
- Mutation in the multidrug resistance MDRI gene (also known as ABCB1-1Δ) can lead to increased risk for severe side effects.
  - Numerous breeds are affected with the MDRI mutation, including various herding breeds, the silken windhound, and the long-haired whippet.
  - Perform MDRI testing.
  - If mutation (heterozygous) is present, major dose reduction is indicated; if patient is homozygous mutant, consider drug omission or substitution.
  - 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.
  - 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.

**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 postadministration.
  - 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.\(^1,2,17-19\)

**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.\(^19\)

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