

Peer Reviewed

Rescue Therapy for Canine Lymphoma

Chemotherapy failure is an obstacle veterinarians frequently encounter when treating non-Hodgkin's lymphoma in dogs.

Although more than 90% of canine patients achieve initial remission with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP-based) treatment protocols,¹⁻⁵ most eventually relapse and require rescue therapy, which is designed to re-induce remission in cases of relapsed lymphoma. Some relapsed dogs become refractory to additional chemotherapy protocols, with lymphoma persisting despite multiple treatment attempts. Cures are rare in patients with relapsed or refractory canine lymphoma.

Because cancer cells become increasingly more resistant to chemotherapeutic agents during the course of therapy, they are more likely to express features of a multidrug resistance phenotype that can arise as a result of⁶:

- Reduced intracellular drug concentration
- Decreased cellular uptake or increased drug excretion
- Up-regulation of inhibitors of apoptosis
- Intracellular or systemic drug detoxification
- Increased expression of cellular damage repair and stress response genes



Lymph node measurement for stage and lymphoma evaluation

Courtesy of Pamela D. Jones, DVM

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Inadequate dosing, wrong frequency, and incorrect route of administration can lead to drug resistance.

Pharmacokinetic or systemic reasons for drug resistance include inadequate dosing, wrong frequency, or incorrect route of administration. Relapses may also occur because cytotoxic drug concentrations are not achieved at specific anatomic sites, such as the central nervous system.⁷

Many drug protocols have been adapted for canine lymphoma in the past 3 decades. Different protocols have varied response rates, durations of remission, and major toxicity events. There is no consensus on optimal rescue therapy. Reported single-agent and multidrug rescue protocols are summarized in **Tables 1** and **2**, respectively.

RESCUE THERAPIES

Relapsed Lymphoma

Novel rescue agents are indicated if the patient fails to achieve a durable remission in the induction phase. Single agents are generally not robust when used for rescue therapy because lymphoma cells are likely to exhibit greater drug resistance than during the induction protocol. The use of single agents increases the likelihood of short remission durations and the risk for up-regulation or drug resistance pathways.

Multidrug protocols generally provide better durations of subsequent remission, as multidrug protocols are inherently associated with higher rates of log cellular cytotoxicity. However, single-agent therapy may provide a reasonable alternative for clients with financial or logistic restrictions.

Many veterinary oncologists administer L-asparaginase at the time that relapse or refractory lymphoma is diagnosed. A previous study demonstrated that L-asparaginase does not prolong the overall duration of remission¹⁷ but can transiently decrease tumor burden by inhibition of protein synthesis.¹⁸ Use of L-asparaginase offers the owner time to consider available rescue therapy options; in addition, the patient may experience improved quality of life for a limited period.

Second Relapse or Refractory Lymphoma

Additional rescue therapy protocols may be initiated to re-induce third or even additional remissions when patients fail rescue therapy. Thorough re-staging for tumor volume should be performed before initiation of subsequent rounds of rescue therapy. Novel drug strategies become harder to design because effective chemotherapeutic drugs have been applied to previous protocols.

Making Rescue Protocol Decisions

A common dilemma faced by clinicians when addressing relapsed lymphoma patients is whether to repeat the original induction protocol or change to a rescue protocol containing novel agents. In theory, cells are less likely to be refractory to drugs with different mechanisms of action.

In our practice, we may re-induce remission with original induction protocols in patients maintained in remission for 6 months or longer prior to relapse after completion of the induction protocol. Conversely, novel drugs or protocols are indicated if the patient has relapsed within 6 months or failed to achieve remission on the induction protocol.

The observed probability of achieving complete or partial remission with a given rescue protocol varies in the literature but generally falls within the 28% to 77% range for a median duration of 40 to 129 days.⁸⁻¹⁶ However, the drugs used in the initial protocol may influence the success of relapse treatment.

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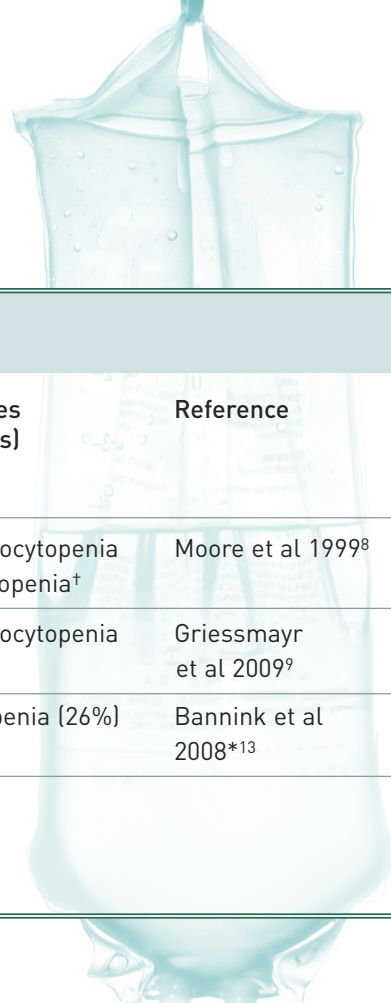


Table 1. Single-Agent Chemotherapy

Protocol	Response Rate* (response/total)	Median Duration of Remission in Days (range)	Toxicoses (% cases)	Reference
Lomustine	28% (11/41)	86 (32–212)	Thrombocytopenia & neutropenia [†]	Moore et al 1999 ⁸
Dacarbazine	35% (14/40)	43 (22–123)	Thrombocytopenia (67%)	Griessmayr et al 2009 ⁹
Dactinomycin	41% [‡] (20/49)	129 [‡] (42–1293)	Neutropenia (26%)	Bannink et al 2008* ¹³

* Complete remission + partial remission

[†] Percent (%) of total cases not provided

[‡] Complete remission only

Table 2. Multidrug Rescue Protocols

Protocol	Response Rate* (response/total)	Median Duration of Remission in Days (range)	Toxicoses (% cases)	Reference
MOPP	65% (76/117)	60 (21–763)	GI (28%)	Rassnick et al 2002 ¹⁰
MPP	34% (14/41)	56 (34–238)	Hematologic & GI [†]	Northrup et al 2008 ¹⁵
DMAC	72% (39/54)	61 (2–467+)	Thrombocytopenia (56%)	Alvarez et al 2006 ¹¹
Lomustine + DTIC	35% (20/57)	62 (34–90)	Neutropenia (26%)	Flory et al 2008 ¹⁴
LCP	77% (37/48)	70 (2–940+)	Hematologic [†]	Saba et al 2009 ¹⁶
A/temozolomide	72% (13/18)	40 (0–217) [‡]	Hematologic & GI [†]	Dervisis et al 2007 ¹²
A/DTIC	71% (25/35)	50 (0–587) [‡]	Hematologic & GI [†]	Dervisis et al 2007 ¹²

* Relapsed canine lymphoma only

[†] Percent (%) of total cases not provided

[‡] All patients were included; remission duration of 0 days means patients did not respond to the protocol

A/DTIC = adriamycin (doxorubicin)/dacarbazine; A/temozolomide = adriamycin/temozolomide; DMAC = dexamethasone, melphalan, dactinomycin, cyclophosphamide; GI = gastrointestinal; LCP = L-asparaginase, cyclophosphamide, prednisone; MOPP = mechlorethamine, vincristine (Oncovin), procarbazine, prednisone; MPP = mechlorethamine, procarbazine, prednisone

Use of L-asparaginase offers the owner time to consider available rescue therapy options.

Subsequent remission periods for each additional rescue attempt have progressively shorter durations.

Traditionally, radiation therapy has been reserved for “crisis” situations that require rapid reduction of localized tumor volume because of the exquisite sensitivity of lymphocytes to the cytotoxic effects of radiation.¹⁹ One study of radiation therapy for canine lymphoma reported a median survival time of 143 days following a 6-fraction protocol in which a total dose of 200 Gy was administered.²⁰

Another study reported a partial response rate of 43% (3/7 dogs) for relapsed lymphoma in dogs treated with low-dose total body irradiation.²¹ In addition, single-node resection or radiation therapy for solitary resistant nodes has occasionally proved beneficial.

BEYOND RESCUE THERAPY

Salvage protocols could be offered at the time of minimal residual disease (MRD) if detection of subclinical malignant cells was feasible before clinical relapse; this could possibly lead to improved long-term survival. Some patients might benefit from treatment interruption, while others might require treatment intensification.²²

In a recent study, thymidine kinase-1 levels measured during chemotherapy demonstrated very clear differences between dogs with lymphoma in complete remission and dogs with lymphoma out of remission.²³ Molecular biological methods such as polymerase chain reaction (PCR) or reverse transcriptase PCR have been applied in veterinary oncology to detect MRD in peripheral blood or lymph nodes for staging purposes.²⁴⁻²⁷ Immunotherapy, including anti-human leukocyte antigen monoclonal antibody and telomerase targeting vaccination, has been described in limited clinical trials.^{28,29}

Improvements in chemotherapy protocols, availability of new effective agents in veterinary oncology, and creation of robust preclinical biomarker assays will collectively improve future outcomes for dogs diagnosed with lymphoma.

See Aids & Resources, back page, for references & suggested reading.



MRD = minimal residual disease, PCR = polymerase chain reaction