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Rescue Chemotherapy Protocols for Dogs with Lymphoma

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INTRODUCTION

The fundamentals of treating dogs with lymphoma are to induce a remission, maintain a remission, and re-induce a remission ("rescue") after a relapse. *Inducing a complete remission is the most important aspect of treatment.* Many protocols are effective. Single-agent or combination chemotherapy will be appropriate for different owners and different patients under different circumstances. Half-body radiation therapy after induction chemotherapy may improve outcome for dogs with lymphoma and studies are currently underway.

Currently, multi-drug protocols that treat dogs for approximately 6 months are sufficient. There does not seem to be any benefit to continuing maintenance therapy beyond this time. The L-CHOP (L-asparaginase, cyclophosphamide, doxorubicin, vincristine, prednisone) is the most successful multi-drug protocol used as first-line treatment for dogs with lymphoma. The overall remission rate is 90% (80% complete remission, 10% partial remission). In general, the median duration of the first remission is 9 months and the overall median survival time is approximately 1 year. Twenty-five % of dogs are long-term survivors; living 2+ years. The factors that are associated with a decreased chance for remission, shorter first remission duration and short survival time are advanced stage, substage b (clinically ill at presentation) and T-cell immunophenotype.

Rescue therapy attempts to establish remission in a patient that has failed first-line treatment or to re-establish remission in a patient that has relapsed after previous treatment. Dogs will relapse following chemotherapy for the following reasons: (1) inadequate dosing and frequency of administering chemotherapy (due to clinician? due to owner?); (2) development of multi-drug resistance; (3) failure to achieve high concentrations of chemotherapy drugs in certain sites, such as CNS. Emergence of drug-resistant tumor clones is by far the most common reason for relapse.

THE RULES OF LYMPHOMA RESCUE

1. First remission duration and survival times are much longer for dogs achieving CR (complete remission; 100% reduction in tumor burden) compared to PR (partial remission; >50%<100%). If dogs do not achieve CR to the scheduled protocol, rescue protocols should be considered.
2. Once the patient achieves CR, each drug should be able to maintain the remission for 3-4 weeks. When the patient relapses, drugs used within 3-4 weeks are no longer effective. Insure that all drugs in the initial protocol are no longer effective and then move on to rescue.

3. Nearly all dogs that successfully complete the initial protocol will experience a relapse. If the time interval between the last treatment and relapse was greater than 4 weeks, re-induction with the same drugs used initially should be attempted first. If the re-induction is successful, the protocol should be continued (see comments about L-asparaginase and doxorubicin below). If the re-induction fails, rescue protocols should be started.
4. If the time interval between the last treatment of the initial protocol and relapse was short (< 4 weeks), it is unlikely that a remission will be induced with more of the same drugs, so rescue protocols should be given to attempt to induce a 2nd remission.
5. In general, the likelihood of response to a rescue protocol and length of the response are half that encountered in the initial therapy.
6. It is reasonable to offer rescue drugs and regimens for as long as the patient continues to feel well. In reality, this may only be 1-3 different protocols.

RESCUE DRUGS AND PROTOCOLS

L-asparaginase

L-asparaginase is generally incorporated into most first-line protocols for canine lymphoma. It is unclear, however, if use of L-asparaginase significantly increases the overall response rate or first remission duration. If an individual patient has achieved either CR or PR after L-asparaginase during the first protocol or after re-induction with the first protocol, then I generally begin rescue regimens with another treatment with L-asparaginase. Repeated courses of treatment with L-asparaginase increases the risk for a hypersensitivity reaction. Diphenhydramine (2mg./kg IM) should be given prior to future doses of L-asparaginase if the dog has already received the drug during a different protocol.

CCNU (Lomustine)

CCNU is an oral alkylating agent. It is a logical choice to rescue dogs with lymphoma since alkylating agents rarely have cross-resistance to each other. CCNU is administered at 70-90 mg/m^2 PO q 4 weeks. CCNU is one of the most myelosuppressive chemotherapy agents used in dogs. Severe neutropenia is likely to occur approximately 7 days after treatment. Other potential major side-effects include hepatotoxicity and cumulative thrombocytopenia. Prophylactic antibiotics are recommended and CBC should be evaluated on days 7 and 28 after treatment. For dogs with neutrophil nadirs < 500 neutrophils/µL, subsequent doses are reduced. Liver enzymes need to be monitored every 2 months. CCNU should be discontinued if ALT increases 3x the upper limit of normal. If CCNU is withheld due to rising ALT, then liver values should be rechecked in 2 weeks and if the changes in ALT resolve, therapy with CCNU can be cautiously continued. If ALT is persistently elevated and there are no other therapies available for the patient, CCNU can be cautiously continued as long as serum bile acid tests are normal. Cumulative thrombocytopenia occurs more commonly when CCNU dosing intervals of less than every 4 weeks are used. CCNU should be discontinued if CBCs show a progressive decrease in platelets.

Moore et al (J Vet Intern Med 1999;13:395) evaluated CCNU to rescue 43 dogs with lymphoma that had relapsed or failed to achieve CR to previous chemotherapy. The overall response rate was 27% for a median of 86 days. Seven percent of the dogs had a CR for a median of 110 days (range, 60-212d) and 20% had a PR for a median of 75 days (range, 36-211d).

Combining two or more alkylating agents might be effective to improve efficacy to rescue dogs with lymphoma. As a class, alkylating agents share a common target (DNA). However, due to differences in pharmacokinetic features, lipid solubility, membrane transport activities, specific enzymatic reactions and specific sites of alkylation, there is significant rationale to try to safely combine agents. For example, the major target for cyclophosphamide is the N-7 position of guanine while that for CCNU is the O-6 position. Cytoxan is carried into cells by active transport mechanisms and in contrast, highly lipid-soluble CCNU enters cells by passive diffusion. We have treated 68 dogs with refractory lymphoma with a protocol to combine CCNU and cytoxan. Another potential combination of alkylating agents is CCNU-DTIC. DTIC is non-classical alkylating agent (covalently binds to biological macromolecules). The key site of DNA attack for CCNU and DTIC is probably similar (O-6 position of guanine) but there is evidence of synergism when the two agents are used together. We have treated 57 dogs with a protocol to combine CCNU with DTIC.

MOPP Chemotherapy

The MOPP protocol was one for the first successful drug regimens to treat people with Hodgkin's and non-Hodgkin's lymphoma. The protocol consists of mechlorethamine (Mustargen, 3.0 mg/m^2 IV), vincristine (0.7 mg/m^2 IV), prednisone (40 mg/m^2 PO q24hr x 14d), procarbazine (50 mg/m^2 PO q24hr x 14d) on day 0 and mechlorethamine (Mustargen, 3.0 mg/m^2 IV), vincristine (0.7 mg/m^2 IV) again on day 7. The cycle is repeated continuously every 28 days as long as a CR or PR is achieved.

In 2002 (J Vet Intern Med 2002;16:576) we evaluated the efficacy of the MOPP protocol when used as a rescue regimen in 117 dogs with lymphoma. The overall response rate for rescue of dogs with lymphoma was 65% for a median of 33 days. Thirty-one percent of dogs had a CR for a median of 63 days (range, 27-763d) and 34% had a PR for a median of 47 days (range, 21-231d). Interestingly, 12% of dogs had response durations longer than their first remission duration. Dogs may initially respond to MOPP (CR or PR), relapse between days 7 and 28, and subsequently respond again to another treatment with MOPP. Clinicians that use the MOPP protocol for rescue of dogs with lymphoma should not be discouraged, even if there is an apparent relapse in the 3-week rest period between cycles. However, it is important to closely monitor lymph node size because if at any time, the disease-burden increases beyond that from the initiation of the MOPP protocol, then the protocol should be discontinued. Also of note, 16% of dogs may have stable disease (SD) when

treated with MOPP (median duration, 33 days; range, 27-476 days) and 20% of these dogs have SD longer than their first remission duration. For this reason, it is not unreasonable to continue MOPP for dogs with SD as long as the patient's quality of life is good and alternative effective protocols are not available.

Mechorethamine (Mustargen®) is often not available or difficult to obtain. Recently, the product has been sold to a different pharmaceutical company so the price has greatly increased. We substitute actinomycin-D (Dactinomycin, Cosmegen®) at 0.5mg/m^2 IV on days 0 and 7 when otherwise Mustargen would have been administered. Since November 1998, we have treated 33 dogs with the DOPP protocol.

DTIC/Doxorubicin

DTIC (Dacarbazine) is an alkylating agent that has activity against lymphoma and possibly sarcomas. Responses seen with DTIC/Doxorubicin protocol may be due to DTIC alone or possibly synergism with doxorubicin. Van Vechten et al (J Vet Intern Med 1990;4:187) evaluated the combination in 15 dogs with relapsed lymphoma. The reported overall response rate was 53% (33% CR and 20% PR). When combining the two drugs, doxorubicin is administered slowly over 30 minutes at 30 mg/m^2 IV (for dogs > 1m^2) or at 1 mg/kg IV (for dogs < 1m^2). DTIC is administered at 800 mg/m^2 IV. The DTIC dose is diluted in 250-1,000 ml 0.9% NaCl and given slowly IV over 5 hours. Since acute and delayed vomiting is a potential side-effect of DTIC, we administer dolasetron (Anzemet®) at 0.6 mg/kg IV immediately before DTIC and send patients home with oral metoclopramide for 7 days. A CBC should be rechecked on day 7 after treatment and the protocol can be repeated on day 21 if the dog achieves CR or PR. Due to the potential for cardiotoxicity, when the dog's lifetime cumulative dose of doxorubicin exceeds 180 mg/m^2, consultation with a cardiologist is recommended to insure that continued treatments are safe.

Mitoxantrone

Mitoxantrone is anthracenedione and has a similar mechanism of action to that of doxorubicin. Activity is considered inferior to doxorubicin and it can be expensive for large dogs. Dogs that have failed multi-agent protocols, including doxorubicin, have been reported to respond to mitoxantrone. The reported response rates for canine lymphoma rescue range from 25 to 45% for medians of 3-4 months. Mitoxantrone is administered at 6 mg/m^2 IV q 2-3 weeks. A CBC should be rechecked on day 7 after treatment and the protocol can be repeated on day 14 or 21 if the dog achieves CR or PR. We have an ongoing study to evaluate the combination of DTIC with mitoxantrone to improve the response rate for dogs with refractory lymphoma.

Other Rescue Options

The DMAC protocol, vinblastine, cisplatin, and radiation therapy may be additional options for some dogs with relapsed lymphoma. Results of ongoing studies with these rescue regimens will be presented.