

MANAGING DOGS WITH LYMPHOMA IN PRIVATE PRACTICE

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CANINE LYMPHOMA: INCIDENCE + SIGNALMENT

Lymphoma (malignant lymphoma, lymphosarcoma) represents 5-10% of all canine tumors and is one of the most common cancers diagnosed and treated in clinical practice.

The annual incidence of lymphoma in dogs is thought to be 13-30 per 100,000 dogs. Dogs of all ages are affected, but lymphoma is predominately diagnosed in middle-age dogs. The median age of dogs with lymphoma has been reported to vary from 5-9 years (range < 6 months to 15 years). There does not seem to be a gender predilection. Recent advances have improved our understanding of the genetic basis of cancer, but there is still much to learn about the genetic factors that define risk for developing lymphoma. Breeds of dogs that have an increased relative risk for lymphoproliferative diseases include Airedale Terriers, Australian Shepherds, Basset Hounds, Boxers, Cavaliers, Shar-Peis, Cockers, Doberman Pinchers, Golden Retrievers, Irish Wolfhounds, Rottweilers, Shih Tzus, Siberian Huskies and Scottish Terriers.

CANINE LYMPHOMA: CLINICAL FEATURES

Clinical features of lymphoma are variable, depending among other factors on the stage (localization) of the disease. The majority of dogs present with non-painful, generalized peripheral lymphadenomegaly. Many dogs are asymptomatic, but owners notice increases in lymph node size. When dogs are systemically ill from lymphoma, clinical signs are varied but may include anorexia, weight loss, vomiting, diarrhea, melena, cough, dyspnea, exercise intolerance and polyuria/polydipsia.

Physical exam findings are generally consistent with organ infiltration by neoplastic lymphocytes. Up to 80% of dogs with lymphoma will present with non-painful **generalized lymph node enlargement**. Abdominal palpation may reveal splenomegaly/hepatomegaly, masses (mesenteric lymph nodes, GI masses) and effusion. Thoracic auscultation may reveal abnormal lung sounds, due to pleural effusion or pulmonary infiltrates. Up to 40% of dogs with lymphoma may have ocular changes including uveitis, thickened iris, hypopyon, hyphema, posterior synechia, glaucoma, vitreous hemorrhage, retinal detachment or infiltration of the optic nerve. These ocular changes are not necessarily all due to infiltration by lymphoma cells. Some may represent paraneoplastic immune-mediated disease.

Cutaneous lymphoma may appear as a primary cutaneous disease or as a part of multisystemic involvement. Lesions are usually generalized or multifocal. Tumors occur as nodules, plaques, ulcers, erythroderma and exfoliative dermatitis. Pruritis occurs frequently. Oral mucosal involvement may also be seen. Histologically, cutaneous lymphoma can be divided into epitheliotropic (T-cell, Mycosis Fungoides) and non-epitheliotropic (usually B-cell). Cutaneous lymphoma is categorized as “stage V” (see below). In general, the prognosis for response to chemotherapy and remission duration is very poor.

Both central and peripheral **nervous system lymphomas** occur in dogs. Neural lymphoma may appear as a primary disease, as part of multisystemic involvement or as a site of relapse of previously diagnosed and treated patients. Neural lymphoma is categorized as “stage V” (see below). In general, the prognosis for response to chemotherapy and remission duration is very poor.

Gastrointestinal lymphoma may appear as solitary masses, diffuse gastrointestinal involvement, or as part of multisystemic involvement. GI lymphoma is categorized as “stage V” (see below). In general, the prognosis for response to chemotherapy and remission duration is very poor.

CANINE LYMPHOMA: DIAGNOSTIC EVALUATION + CLINICAL STAGING

Staging is defined as evaluating the “extent of disease” based on physical examination, lab testing, imaging and cytology of tissues and bone marrow. Canine lymphoma is staged and substaged based on criteria established by the World Health Organization (WHO).

World Health Organization (WHO) Clinical Staging System for Canine Lymphoma

	STAGE:
I	Single lymph node involved
II	Regional lymph nodes involved (same side diaphragm)
III	Generalized peripheral lymph node involvement
IV	Liver and/or spleen (+/- stages I-III)
V	Blood, bone marrow, extranodal (+/- stages I-IV)
	SUBSTAGE:
a	No signs of systemic illness
b	Signs of systemic illness, hypercalcemia, uveitis, fever

The **goals of cancer staging** are to:

1. **impart an accurate prognosis** to owners
 - a. Use of “lymphoma stage” as a prognostic factor has been inconsistent and controversial throughout published studies. However, in general, dogs with stage I or II have higher remission rates, longer remission durations and longer survival times compared to those dogs with stage III, IV or V lymphoma. Certain anatomic locations within stage V have a much worse prognosis. For example, gastrointestinal, cutaneous and neural lymphoma respond poorly to chemotherapy and dogs that respond may still have a relatively short remission durations or survival times. Pulmonary involvement categorizes dogs into stage V. Interestingly, however, pulmonary infiltrates alone do not appear to influence the prognosis. On the other hand, presence of any lymph nodes within the cranial mediastinum may be an independent negative prognostic factor. For example, dogs with anterior mediastinal masses (AMM) have shorter remission duration and survival times.
2. **choose an appropriate treatment regimen**
 - a. Lymphoma is generally considered a systemic disease, and as such, is most often best treated by use of systemic chemotherapy. However, cases of localized lymphoma may occur and may be better treated with surgery, radiation or a combination of these methods. Careful attention to staging results is needed when working-up patients with suspected localized lymphoma to offer the most appropriate treatment.
 - b. Urgent situations such as a neoplastic pleural effusion may be diagnosed and may need to be addressed, for example with thoracocentesis, as part of the initial treatment regimen. Occasionally, other disease processes are identified during staging. These may need to be closely monitored during therapy and they may or may not effect the owner’s decision to treat at all.
 - c. Selection of chemotherapy agents and protocols may be limited by specific organ toxicities. For example, cyclophosphamide may cause sterile, hemorrhagic cystitis. The risk for this adverse effect is higher in dogs with concurrent bladder disease. For this reason, baseline screening of the urine with a urinalysis is essential. Culture of the urine sample should be done if indicated based on results of the UA. Doxorubicin may be associated with cardiotoxicity, specifically arrhythmias and dilated cardiomyopathy. Depending on physical exam of the cardiovascular system (and possibly breed-risk), consultation with a cardiologist for an echocardiograph may be indicated to determine the safety of including this drug in the treatment regimen. Finally, hepatic and/or renal clearance may be important for some chemotherapeutics. These drugs may still be used in patients with altered hepatic or renal function, but adjustments in dosage or interval may be necessary.

3. have a **baseline** prior to starting therapy
 - a. The fundamentals of treatment of lymphoma are to induce a remission, maintain a remission, and re-induce a remission (“rescue”) after a relapse. *Inducing a **complete remission (CR)** is the most important technical aspect of treatment.* Dogs that achieve CR to combination chemotherapy have significantly longer survival times compared to dogs that only achieve a partial response or no response. Baseline staging test results are used to determine if sites affected with lymphoma appropriately respond to therapy. If CR does not occur to the scheduled protocol, additional drugs or protocols should be considered.

Which tests should be done to stage dogs with lymphoma?

Bottom line: don’t regret not having complete staging information or an accurate diagnosis prior to initiating treatment!

Complete staging for dogs with lymphoma **includes** complete blood count, biochemistry panel, urinalysis, thoracic radiographs, abdominal imaging, bone marrow aspiration cytology and histopathology. Depending on the clinical situation, all of these tests might not be done. It is important to realize that without all of these tests, dogs should be considered “incompletely” staged and using previously reported information about the value of lymphoma stage and outcome of dogs treated with a particular protocol might not be accurate. Stage migration refers to the addition of more sensitive tests and subsequently identifying previously undetectable lesions. Dogs are then moved (or migrated) into higher stage categories.

1. Complete blood count (CBC) – *bare-minimum part of data set for all dogs with lymphoma.* Dogs should have a CBC evaluated by a clinical pathologist to screen for circulating lymphoblasts. Although many automated hematology machines correlate very well with sophisticated analyzers in labs, they will not pick up low levels of circulating lymphoblasts.
2. Biochemistry profile – *bare-minimum part of data set for all dogs with lymphoma.* Baseline evaluations of organ function and evaluate for paraneoplastic hypercalcemia.
3. Urinalysis - *bare-minimum part of data set for all dogs with lymphoma.* Urinary tract infections (symptomatic or occult) can increase the risk for sepsis with administration of chemotherapy drugs. Glomerulonephritis might be present.
4. Thoracic radiographs - *bare-minimum part of data set for all dogs with lymphoma.* Up to 85% of dogs will have abnormalities detected by radiographs. Possible findings include lymph node enlargement (mediastinal, sternal, tracheobronchial), mediastinal masses (thymic lymphoma vs. mediastinal lymph nodes), pleural effusion and pulmonary infiltrates (interstitial, alveolar, reticulo-nodular (miliary). 2-view thoracic radiographs are sufficient in the majority of cases since nodular patterns are uncommon.
5. Abdominal imaging – Abdominal radiographs are generally appropriate as a baseline evaluation of organ size however, abdominal ultrasound is more sensitive. Abdominal ultrasound should be done if dogs present with gastrointestinal (GI) signs to rule out GI lymphoma, GI obstruction and/or pancreatitis). In addition, abdominal ultrasound is recommended as a baseline in dogs with renal or hepatic insufficiencies and in debilitated patients.
6. Bone marrow aspiration cytology - Presence of a normal CBC *does not* rule out bone marrow involvement. Only ½ of dogs with bone marrow involvement with lymphoma will have changes in peripheral blood (i.e. circulating lymphoblasts). Bone marrow aspiration is part of complete staging information and is strongly recommended for dogs with baseline cytopenias (neutropenia, thrombocytopenia) prior to initiating therapy.

Is a histopathology needed to confirm the diagnosis?

The majority of canine lymphomas are diffuse high (65%) or intermediate (20%) grade. In general, for dogs with high-grade B-cell lymphoma, there is an excellent correlation between a cytomorphologic and histomorphologic diagnosis. For some intermediate-grade lymphomas and for dogs with low-grade or mixed-cell lymphomas, the correlation might not be that good. For dogs with presenting with typical clinical signs of lymphoma (specifically, dogs with generalized lymph node enlargement), diagnosing lymphoma based on cytology of fine needle aspirates interpreted by a trained cytopathologist is appropriate. For all other cases, a cytological diagnosis of lymphoma should be confirmed with histopathology. Histopathology can also provide information in terms of the tumor grade and immunophenotype (see “prognostic factors”, below). Tru-Cut®, needle core, or incisional lymph node biopsies are generally adequate for most patients. For dogs with solitary (stage I) or regional lymph node (stage II) enlargement, surgical excision of an entire node is preferable. Low-grade histology is often found in dogs with stage I or II disease and is best-diagnosed based on architecture as well as morphology. Acute leukemia (lymphoid and myeloid) is of bone marrow or splenic origin and can secondarily invade lymph nodes. Finding mild to moderately enlarged lymph nodes in a dog with circulating “blasts”, cytopenias or both should raise the suspicion of acute leukemia. Also, many dogs with acute myeloid leukemia might have mediastinal masses. In addition to other diagnostic tests for a suspect leukemia (flow cytometry, cytochemistry), acquiring a sample of the lymph node for histology before simply assuming the patient has lymphoma is most appropriate.

CANINE LYMPHOMA: CHEMOTHERAPY OPTIONS

Canine lymphoma is a systemic disease and as such **chemotherapy** is the **most appropriate** treatment modality. The systemic nature of lymphoma in dogs has limited the usefulness of radiation therapy. However, lymphocytes are extremely sensitive to radiation therapy. For this reason, radiation has a role in the treatment of lymphoma in certain situations. Examples include palliative therapy to relieve signs associated with enlarged lymph nodes, emergency therapy for airway obstruction, stage I lymphoma, focal cutaneous lesions, nasal lymphoma, solitary bone lesions, CNS lymphoma, total body irradiation with bone marrow transplantation and half-body irradiation. Half-body radiation therapy after a course of chemotherapy is currently being investigated as a means to increase remission duration compared to chemotherapy protocols alone. Results of controlled studies might indicate if this is the case.

When treated with chemotherapy, dogs with lymphoma are not cured. However, chemotherapy can produce resolution of most or all of the clinical signs and laboratory abnormalities seen at presentation for many months without compromising quality of life. The fundamentals of treatment of 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 technical aspect of treatment.* There are many protocols that are effective for the treatment of lymphoma in dogs. Single-agent or combination chemotherapy will be appropriate for different owners and different patients under different circumstances.

Terminology:

Induction chemotherapy – beginning period of treatment, intensive portion of the protocol to achieve a remission.

Maintenance therapy – intermittent treatment (every 2-3 weeks) to maintain remission.

Relapse – recurrence of clinical signs.

Rescue – attempt to induce a second remission after relapse. Generally involves using new drugs. Depending on initial protocol, rescue may involve first attempting returning to start of the protocol.

Remission – resolution of clinical signs and laboratory abnormalities. Remission status is defined as CR, PR, SD, PD (see below). Always measure lymph nodes prior to starting therapy. Once the cancer is in remission, it is important to re-evaluate all of the parameters that were abnormal at initial staging. Median first remission duration and survival times are much longer for dogs achieving CR compared to PR. For this reason, if dogs do not achieve CR to the scheduled protocol, additional drugs should be considered.

Response or Remission Status

	Response	Definition
CR	Complete Response	100% reduction in size of all measurable disease
PR	Partial Response	> 50% reduction but < 100% reduction
SD	Stable Disease	< 50% reduction or no change in size of all measurable disease and lack of appearance of new neoplastic lesions
PD	Progressive Disease	Increase of > 25% in the size of all measurable disease or the appearance of new neoplastic lesions.

A. **No Treatment** - Survival for dogs without treatment is typically 30 days (median).

B. **Prednisone alone** - A palliative option (40 mg/m² PO daily X 7 days then EOD).

1. Decision to use prednisone alone needs to be considered seriously. Prior use of steroids may affect response to other drugs. This may occur because when dogs are evaluated, they may be erroneously staged or perhaps prednisone induces multidrug resistance.
2. Remission rate – 50%.
3. Survival – 30-60 days (median).

C. **Multidrug Protocols**

1. A wide variety of protocols have been described. In general, results with single-agent chemotherapy protocols are less optimal than those with combinations of drugs.

COP

1. Cyclophosphamide, Vincristine, Prednisone
2. Remission rate – 60-75%.
3. 1st remission duration – 4-5 months (median)
4. Survival – 6 months (median), 10-20% 1-year.
5. Why choose COP? Clinician preference, only 3 drugs to feel comfortable with. Note: the length of the protocol is 1 year!

Single-Agent Doxorubicin

1. Doxorubicin (Adriamycin) is the single most effective drug for treatment of lymphoma in dogs. In general, combination chemotherapy is the most widely used approach and is considered the most efficacious. However, single-agent doxorubicin (q 3 weeks) is a reasonable treatment option for some dogs.
2. Remission rate – 75-85%.
3. 1st remission duration – 6 months (median)
4. Survival – 6-9 months (median).
5. Beware of statements that results are same as CHOP-based protocols: initial remission rate is lower, and chance for long-term remission/survival is less.

Doxorubicin, L-asparaginase- containing Protocols

1. Numerous protocols exist and can be found in veterinary oncology textbooks and in journal articles.
2. VELCAP - Vincristine, Elspar, Cyclophosphamide, Adriamycin, Prednisone
3. CHOP – Cyclophosphamide, Hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), Prednisone + L-asparaginase.
4. Highest response rates and longest remission durations have been with 5-drug protocols
5. Remission rate – 80-95%.
6. 1st remission duration – 9-10 months (median)
7. Survival – 1 year (median), 25% 2-year.

D. Is **maintenance chemotherapy** needed?

1. Currently, multidrug protocols that treat dogs for approximately 6 months are thought to be sufficient.
2. If dogs relapse during the protocol, rescue therapy is needed.
3. If dogs relapse after completion of the protocol, then most often rescue therapy involves first returning to beginning of the protocol and attempting re-induction. If re-induction of the same protocol is successful, then dogs should continue on the protocol and *then remain on maintenance therapy*. Generally, a COP protocol would be recommended as a maintenance protocol after a dog finishes its second round of doxorubicin-based chemotherapy.
4. An initial 6 month protocol without maintenance does not seem to be any less advantageous than simply starting out with a protocol that incorporates a maintenance phase. However, client education is very important:
 - a. Clients need to understand after completion of a 6 month protocol relapse will occur. Only approximately 5% of dogs will not relapse.
 - b. It is not uncommon for some clients not to choose attempting therapy again. Reasons are numerous. An initial protocol with maintenance therapy may be better suited for these clients; however, it is not always simple to determine this at the time of protocol discussion.

E. **Choosing** a chemotherapy protocol

1. Many protocols are effective for the treatment of lymphoma in dogs. Single-agent or combination chemotherapy will be appropriate for different owners and different patients under different circumstances.
2. Only use protocols incorporating drugs that you, your colleagues and your technical staff have adequate training with. Insure everyone understands handling, administering and managing potential side effects of the drugs.
3. Using a protocol in use by an oncologist near your practice is an excellent way to offer a current treatment regimen to your clients and their pets. It is also helpful if you need to seek advice regarding response to the drugs or protocol. An ideal collaboration would be to refer the dog to an oncologist for the initial evaluation and induction. Once the dog has received all of the drugs in the protocol, there is a better understanding of the potential for that patient to experience side effects, and once the dog is in remission, then having some of the treatments done by the primary care veterinarian is an excellent collaborative approach.

F. Using **chemotherapy in private practice** and being able to sleep at night

1. Only use protocols incorporating drugs that you, your colleagues and your technical staff have adequate training with. Insure everyone understands handling, administering and managing potential side effects of the drugs.
2. Common clinical situations you may encounter:
 - a. Does the dog need emergency chemotherapy? Sick dogs (substage b) will present with anorexia, vomiting and diarrhea among many other clinical signs. In general, sick dogs with lymphoma dramatically improve with supportive care (IV fluids, antibiotics, gastric protectants). Improving organ perfusion and overall patient condition is essential prior to initiating chemotherapy. Don't rush chemotherapy! Dogs that are severely dyspneic (due to lymph nodes obstructing upper or lower airways or perhaps thoracic cavity involvement such as effusion or infiltrates), have severe hypercalcemia or bleeding diatheses need to receive treatment as soon as possible. Supportive therapies (generally before treatment) are still essential!
 - b. Obese dogs – dosing drugs based on actual body weight may cause excessive toxicity in dogs that are very overweight. However, there are no precise adjustments to be made based on obesity. A general recommendation would be to dose based “ideal” body weight for dogs that are “obese” (body condition score 8 of 9 – ribs not palpable under very heavy fat, heavy fat deposits over lumbar area and based of tail, waist absent) or for dogs that are “grossly obese” (body condition score 9 of 9 – massive fat deposits over thorax, spine and base of tail, waist absent, fat deposits on neck and limbs).

- c. Neutropenia – During *weekly* chemotherapy, it is fairly common for dogs to be neutropenic when they are due for their next treatment. For most lymphoma protocols, it is adequate to treat with chemotherapy as long as the neutrophil count is $\geq 2,000$ cells/ μ L. This is a general guideline for treatments during weekly induction. If neutropenia occurs, rechecking the CBC in 3 days is recommended to not delay treatment for too long. Neutropenia identified 2-3 weeks after a treatment may be due to individual patient variation or underlying bone marrow disorder. Be cautious.
- d. Hepatic insufficiency – some dogs might have liver disease either due to underlying hepatic lymphoma or perhaps a preexisting condition. In terms of common lymphoma protocols, vincristine needs to be used cautiously. An automatic dose reduction to 0.5 mg/m² is recommended. L-asparaginase combined with vincristine is a common start to many lymphoma protocols. The combination of L-asparaginase with concurrent vincristine can lead to excessive toxicity in the presence of liver failure. In general, I recommend giving vincristine and then follow with L-asparaginase at a minimum of 3 days later
- e. Neutropenia (baseline) – occasionally, some dogs may have a baseline neutropenia either due to myelophthisis or splenomegaly. Immune-mediated paraneoplastic neutropenia can also be a possible cause. L-asparaginase combined with vincristine is a common start to many lymphoma protocols. The combination of L-asparaginase with concurrent vincristine can lead to excessive toxicity in dogs that are already severely neutropenic. In general, if the baseline neutrophil count is $< 1,500$ cells/ μ L, I would recommend giving vincristine and then follow with L-asparaginase at a minimum of 3 days later.
- f. Lymph nodes are not shrinking. When is it time for alternative treatments? See Rescue Chemotherapy (below).
- g. Lymph nodes have enlarged again. Don't continue with current protocol. See Rescue Chemotherapy (below).

CANINE LYMPHOMA: PROGNOSTIC FACTORS

Prognostic factors are variables that independently influence the response rate and duration to a particular treatment. Prognostic factors are used to help guide treatment decisions by educating owners about realistic expectations for their pets. It is important to remember that prognostic factors are based on statistics, and most often presented as the “median” dog. Fifty % of dogs will live for a shorter period but also, 50% may survive longer. Despite negative prognostic factors, long term survival may be possible so it is almost never wrong to offer an opportunity of treatment to owner's of dogs with lymphoma.

A. Immunophenotype

1. The majority (75%) of canine lymphomas are of B-cell origin and the remaining 25% are of T-cell origin.
2. Phenotype is one of the most important prognostic factors.
3. T-cell: lower remission rate, shorter remission duration, shorter survival time.
4. B-cell: higher remission rate, longer remission duration, longer survival time.

B. Stage

1. Inconsistent and controversial throughout studies.
2. In general, in terms of remission rate, remission duration and survival stage I + II >>> III, IV, V.
3. Certain anatomic locations within stage V have a much worse prognosis
 - a. gastrointestinal, cutaneous, neural lymphoma – in general, poor response to chemotherapy and relatively short remission durations/survival times.
4. Pulmonary involvement – historically has categorized dogs into stage V. However, see below.

C. Substage

1. Dogs in substage b are less likely to achieve remission and will have shorter remission durations and survival times.

D. Hypercalcemia

1. Significantly shorter survival time. Most likely related to T-cell phenotype

E. Response to Treatment

1. Dogs that achieve a complete remission to combination chemotherapy have significantly longer survival times compared to dogs that only achieve a partial response or no response. For this reason, if dogs do not achieve CR to the scheduled protocol, additional drugs should be considered.

F. Pretreatment with Steroids

1. Prior treatment with corticosteroids has been shown to negatively affect prognosis (less likely to respond to combination chemotherapy, decreased survival time).
2. May be due to misinterpreting staging information (i.e. “down-staging”).
3. May be due to development of multi-drug resistance.

G. Histologic Grade

1. The majority of lymphomas in dogs are intermediate-high grade (>85%).
2. Intermediate-High-grade - higher frequency of complete responses to chemotherapy, shorter remission duration, shorter survival time.
3. Low-grade - generally do not respond quickly to chemotherapy, may only respond partially when treated, may survive long time with less aggressive chemotherapy.

H. Pulmonary Involvement

1. Thoracic abnormalities are very common in dogs with lymphoma (see above).
2. Pulmonary infiltrates have historically categorized dogs into stage V. However, pulmonary infiltrates alone do not appear to influence the prognosis.
3. Presence of any lymph nodes within the cranial mediastinum may be an independent negative prognostic factor. Dogs with anterior mediastinal masses (AMM) have shorter remission duration and survival times.

I. Dose Reductions

1. Treating patients with drugs used at their maximally tolerated dosage is a major principle of cancer therapy
2. Dose reductions are important to avoid unacceptable toxicity in a patient, but unnecessary reductions of chemotherapy dosages might lead to a worse prognosis.

RESCUE CHEMOTHERAPY PROTOCOLS FOR DOGS WITH LYMPHOMA

During a successful chemotherapy protocol, dogs should never have recurrence of clinical signs. If clinical signs recur, it is considered a relapse. Dogs will relapse following chemotherapy for the following reasons:

1. development of multi-drug resistance – by far the most common cause for relapse
2. inadequate dosing and frequency of administering chemotherapy (due to clinician? due to owner?)
3. failure to achieve high concentrations of chemotherapy drugs in certain sites, such as CNS.

A. The **rules** of lymphoma rescue

1. First remission duration and survival times are much longer for dogs achieving CR compared to PR. For this reason, 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 of their lymphoma. 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 and then dogs should remain on maintenance therapy. 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.

B. Rescue drugs and protocols

1. The following drugs or protocols are frequently used to rescue dogs with lymphoma. It is beyond the scope of this lecture to detail the use of these options. Consultation with an oncologist or referral is strongly recommended to decide on the best course of action for a dog with refractory lymphoma.
 - L-asparaginase
 - CCNU (Lomustine)
 - MOPP Chemotherapy
 - DTIC alone or in combination with other agents
 - Mitoxantrone