Diagnosis
Before instituting therapy, the clinician must confirm the diagnosis cytologically, histopathologically, or, less frequently, using molecular techniques. In addition, a minimum database consisting of a CBC, serum biochemistry profile, and urinalysis should be obtained if the owners are contemplating treatment.

In most cats and dogs with multicentric, superficial extranodal, mediastinal, or alimentary lymphoma, a diagnosis can easily be obtained by cytologic evaluation of FNA of the affected organs or lymph nodes.

In our practice lymphomas can be diagnosed cytologically in approximately 90% of dogs and 70% to 75% of cats evaluated (i.e., usually in only 10% of the dogs and 25% to 30% of the cats is it necessary to perform a histopathologic, flow cytometric, or molecular evaluation of a lymph node or mass to establish a diagnosis). Until there is conclusive evidence that the histopathologic classification of canine and feline lymphomas offers prognostic information, the surgical removal of a lymph node or extranodal mass for histopathologic evaluation in an animal with a cytologic diagnosis of lymphoma is not indicated. A diagnosis based on cytologic findings rather than histopathologic findings yielded by an excisional lymph node biopsy also offers two major benefits: (1) It is associated with minimal or no morbidity, and (2) it is financially acceptable to most owners.

New diagnostic methodologies commonly used in patients with lymphoma in our clinic include immunophenotyping by flow cytometry (FCM) and clonal analysis by polymerase chain reaction (PCR). In the former, a sample of the affected organ/tissue is obtained by FNA and placed in appropriate transport media. In the laboratory these cells are incubated with specific antibodies that recognize epitopes specific for T- or B-cells. FCM evaluation of the sample allows to immunophenotype the cell population as T- or B-cell derived. Immunophenotyping by flow cytometry is now performed by some diagnostic reference laboratories. Immunophenotyping can also be carried out on lymph node or tissue biopsies immunohistochemically. Clonal analysis by PCR (or PARR, for PCR for Antigen Receptor Rearrangement) also requires an FNA or a small biopsy specimen. Specific laboratories will evaluate the population of cells in question by PCR to determine if they are B- or T-cell in origin and if they are monoclonal or polyclonal. This technique has high sensitivity and specificity for distinguishing reactive lymphadenopathy from lymphoma in dogs, but is not that accurate in cats (Lana et al., 2006). As a general rule, we use FCM to immunophenotype lymphomas, and PARR when the diagnosis of lymphoma is in question (i.e, to confirm or rule out lymphoma).

After a diagnosis of lymphoma is confirmed, it is customary to stage the disease to obtain a prognosis. A staging system devised by the World Health Organization has been used for the past two decades for the staging of cats and dogs with lymphoma. In this system, derived from the TNM (tumor, node, metastasis) staging system for neoplasms in humans, clinical and clinicopathologic information from the patient is used...
in an attempt to determine the extent of disease and correlate it with the prognosis. Unfortunately, it has little prognostic value (i.e., animals with stage I disease have survival times similar to those of animals with stage IV disease). The only prognostic information of clinical relevance in this system is the fact that asymptomatic (i.e., substage a) dogs with lymphoma have better prognosis than “sick” (i.e., substage b) dogs. A staging system that takes into account tumor bulk and FeLV status in cats with lymphoma provides some prognostic information. Until a new system is devised, it is advisable to determine the prognosis on the basis of the patient’s overall clinical condition, the FeLV status (in cats), and any constitutional signs or severe hematologic and biochemical abnormalities the patient may have. Another important issue is that even though a specific staging protocol may be of some prognostic value in patients treated with a given chemotherapy protocol, it may not be so when a different drug combination is used. Moreover, at this time the effectiveness of more aggressive protocols in dogs and cats with advanced-stage lymphoma is unknown.

At least a CBC, a serum biochemistry profile, and a urinalysis should be performed in all cats and dogs with lymphoma whose owners are contemplating therapy. In addition, FeLV and FIV tests should be performed in cats. The resulting minimum database can provide a wealth of information that can help the owner (and the clinician) decide whether to treat the patient. In addition, once a decision to treat the pet has been made, the nature of any clinicopathologic abnormalities usually dictates the treatment or treatments used. For example, in a dog with pronounced cytopenias caused by lymphomatous infiltration of the bone marrow, a highly myelosuppressive chemotherapy combination almost certainly will result in severe neutropenia and sepsis; it should therefore be avoided.

In cats and dogs with suspected CNS lymphoma, it is advisable to perform cerebrospinal fluid (CSF) analysis and advanced imaging (i.e., computed tomography [CT] scan or magnetic resonance imaging [MRI]). The finding of high numbers of neoplastic lymphoid cells and an increased protein concentration in a CSF sample is diagnostic for lymphoma. Because of their poor accessibility, the diagnosis of extradural masses usually requires the collection of a surgical specimen for cytologic or histopathologic evaluation. As discussed above, I assume that any dog or cat with lymphoma and central neurologic signs has CNS involvement until proven otherwise, and we treat them appropriately (see below).

As previously discussed, immunophenotyping of canine and feline lymphoma has become routine for most oncologists. This can be done by immunocytochemistry, immunohistochemistry, flow cytometry, or PARR. But the main question is: should every dog or cat with lymphoma be immunophenotyped prior to initiating therapy? The blanket answer is “no”. Phenotype may change the prognosis (although this is still questionable), but it rarely changes the initial treatment approach in our clinic. In dogs, a T-cell phenotype is quite likely if the patient is a Boxer, has hypercalcemia or a mediastinal mass, or has cutaneous or CNS involvement.

Published reports suggest that dogs with T-cell lymphoma treated with standard combination chemotherapy have a worse prognosis for remission and survival than dogs with B-cell tumors; however, in our experience, this is not the case. In a recent study we demonstrated that T-cell phenotype was not a negative prognostic factor in dogs with lymphoma treated with COP- or CHOP-based protocols (Hosoya et al., 2007).
This is likely because most dogs with T-cell lymphoma received lomustine (CCNU), a drug that in our experience is effective in patients with T-cell phenotype.

**Treatment**

Once a diagnosis of lymphoma is established, the prognosis and potential therapeutic options should be discussed with the pet’s family. Remission rates in cats and dogs with lymphoma treated with various chemotherapy protocols are approximately 65% to 75% and 80% to 90%, respectively. Most cats with multicentric or mediastinal lymphoma treated with multiple-agent chemotherapy protocols are expected to live 6 to 9 months; approximately 20% of the cats live more than 1 year. Cats with small cell intestinal lymphoma typically live >2 years. Most dogs with lymphoma treated with multi-agent chemotherapy are expected to live 12 to 16 months; approximately 20% to 30% of the dogs are alive 2 years after diagnosis. The approximate survival time in untreated cats and dogs with lymphoma is 4 to 8 weeks. Probably the most important reason for the shorter survival times in cats than in dogs with lymphoma is that remissions appear to be difficult to reinduce once the tumor has relapsed. In addition, the retrovirus-associated nonlymphomatous disorders that affect cats with lymphoma lead to shortened survival times (i.e., FeLV infection is a negative prognostic factor in cats with lymphoma).

In my experience, even if an animal has stage I nodal or extranodal lymphoma at the time of presentation, systemic dissemination of the disease usually occurs within weeks to months of diagnosis. However, occasionally solitary oral or cutaneous lymphomas may behave as true stage I diseases (i.e., there is no systemic dissemination). Therefore the mainstay of treatment for animals with lymphoma is chemotherapy, given the fact that lymphomas are (or will become) systemic neoplasms. Surgery, radiotherapy, or both can be used to treat localized lymphomas before or during chemotherapy. Radiotherapy has been used with some degree of success in cats with nasal or solitary epidural lymphoma. Half-body irradiation or chemotherapy and bone marrow transplantation have also been recently used to treat dogs with lymphoma. General guidelines for the management of patients with lymphoma are presented here. I have used the protocols recommended in this chapter with a success rate comparable to those of other treatments published in the literature.

There are two main chemotherapeutic approaches in dogs and cats with lymphoma: induction chemotherapy, followed by maintenance (and reinduction) or more aggressive chemotherapy for a finite period of time, at the end of which no maintenance chemotherapy is used. The former is usually done with a less aggressive COP (cyclophosphamide, vincristine, and prednisone)-based protocol, whereas the latter is usually based on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-type protocols. An example of the latter is one of several University of Wisconsin (UW) protocols. CHOP-based protocols are similar to those used in people with high-grade lymphomas.

**COP-Based Protocols**

When using COP-based protocols, the treatment of cats and dogs with lymphoma is divided into several phases, or strategies: induction of remission, intensification, maintenance, and reinduction of remission or “rescue”. Immediately after diagnosis, a
relatively “nonaggressive” multiple-agent COP-based chemotherapy protocol is used to induce remission; in our clinic we frequently use the COAP protocol, with the addition of subcutaneous cytosine arabinoside to the COP protocol. During this phase, which lasts 6 to 8 weeks, patients are evaluated weekly by a veterinarian, at which time they receive an intravenous (IV) injection of an antimitotic agent (vincristine) in addition to undergoing a routine physical examination (with or without a CBC). If at the end of this phase the patient is considered to be in complete remission (CR; i.e., all neoplastic masses have completely disappeared), the maintenance phase is initiated. During this phase, a multiple-agent chemotherapy protocol consisting of three drugs (chlorambucil [Leukeran], methotrexate, prednisone [LMP]) administered orally is used, so that the patient requires less intensive monitoring (once every 6 to 8 weeks). Over the past few years, we have instructed the owners of dogs with multicentric lymphoma to closely monitor the size of the lymph nodes in their pets; when the nodes start enlarging (i.e., relapse), we add a fourth drug to the LMP protocol (usually vincristine, at a dosage of 0.5-0.75 mg/m2, IV, q1-2 weeks). This usually suffices to reinduce remission and maintain it for several weeks or months.

The maintenance or modified maintenance phase continues until the tumor relapses (i.e., is out of remission), at which time the reinduction phase begins. This phase is similar to the induction phase in that intensive treatments are used. Once remission is obtained, the patient is started again on a modified maintenance protocol. If at the end of the induction phase the patient is not in CR, we recommend that intensification with L-asparaginase be done before the maintenance phase is initiated. In addition to the chemotherapeutic approach discussed in this section, a variety of protocols have been used successfully in the treatment of cats and dogs with lymphoma. (See Suggested Readings for additional information.)

**Induction of remission.** As previously discussed, my protocol of choice for the induction of remission is COP (or COAP). The agents in this protocol consist of cyclophosphamide, vincristine, (cytosine arabinoside), and prednisone; these four drugs are currently available as generic products and are inexpensive. The dosages are specified in Box 80-1. These drugs belong to four different categories, have different mechanisms of action, and do not have superimposed toxicities (with the exception of cyclophosphamide and cytosine arabinoside, both of which are myelosuppressive; however, the latter is used only for a short period). The cytosine arabinoside is usually administered by the subcutaneous (SC) route because, given its short half-life and S-phase–specific mechanism of action, an IV bolus injection results in minimal cell kill; SC administration of this drug is painful in cats (and in some dogs). IV infusion of the agent is also associated with myelosuppression. The induction phase lasts 6 to 8 weeks, and weekly visits to the veterinarian are necessary during this time.

During the induction phase toxicity is minimal (<15%) and client compliance is high because most of the toxic signs are hematologic (i.e., cytopenias) and usually do not result in clinical signs that can be detected by the owners. The dose-limiting toxicity of this induction protocol is hematologic (i.e., myelosuppression leading to neutropenia) and it occurs in <10% of the patients; the neutrophil nadir usually occurs around day 7 or 8 because two myelosuppressive agents (i.e., cyclophosphamide and cytosine arabinoside) are given during the initial 2 to 4 days of treatment. In most cases the
neutropenia is mild (2000 to 3500 cells/µl). The neutropenia is severe if the animals have neoplastic bone marrow infiltration before the initiation of treatment, have FeLV- or FIV-associated myelodysplasia or other retrovirus-associated bone marrow disorders, or receive the cytosine arabinoside by constant-rate IV infusion rather than by the SC route. Also, anecdotally, neutropenia appears to be common in Cocker Spaniels and West Highland White terriers receiving this protocol. Gastrointestinal toxicity is minimal to nonexistent; however, cats receiving cyclophosphamide occasionally become anorectic. Consequently, this drug should be administered once every 3 weeks in cats (as opposed to every other day as in dogs). If anorexia develops, treatment with cyproheptadine, an antiserotonin drug, at a dosage of 1 to 2 mg per cat PO q8-12 hours is indicated. Hair loss is also minimal, and it occurs primarily in woolly-haired dogs (e.g., Poodle, Bichon Frise); cats (and some dogs) may shed their tactile hairs during treatment.

During this phase, owners are instructed to monitor their pet’s appetite and activity level, measure their lymph nodes (if superficial lymphadenopathy was present initially), and take their pet’s rectal temperature daily (pyrexia is usually secondary to neutropenia and bacteremia or sepsis). If pyrexia develops, owners are instructed to contact their veterinarian immediately so that their pet can undergo a complete physical examination and CBC. Treatment with COP results in CR within 1 to 14 days of the start of therapy in most animals (>85% in dogs, >70% in cats). This remission is usually maintained throughout the induction phase.

In dogs with diffuse alimentary lymphoma we use a more aggressive doxorubicin-containing protocol (CHOP) because, in my experience, the response rate to COAP is low. This protocol is more expensive and more likely to cause adverse effects than the COAP protocol. We typically use lomustine (CCNU) in dogs with epidermotropic T-cell lymphoma, and as part of the maintenance or reinduction protocol in dogs with other large T-cell lymphomas.

In dogs and cats with multicentric (or any other anatomic form of) lymphoma coexisting with neurologic signs, we usually use the COAP protocol but administer the cytosine arabinoside as a continuous IV infusion (200-400 mg/m² as an IV infusion over 24 hours for 1 to 4 days) in order to attain high concentrations of this drug in the CNS. This protocol tends to cause marked myelosuppression in cats, so we typically administer cytosine arabinoside as a 12- to 24-hour infusion (200 mg/m²) in this species. More information on the treatment of dogs and cats with suspected or confirmed CNS lymphoma is given later in this chapter.

Maintenance. The protocol recommended for the maintenance phase of treatment is LMP (“lump”), which consists of chlorambucil, methotrexate, and prednisone. These drugs also act by three different mechanisms of action and have different toxicities. The advantages of this protocol include its reduced cost compared with the cost of the induction phase; its ease of administration (all the drugs are administered orally by the owners); its minimal toxicity; and the fact that intensive monitoring by a veterinarian is not necessary. Chlorambucil can now be compounded at a very low cost to the owners.

The toxicities associated with LMP maintenance chemotherapy are minimal. Of the three drugs in this protocol, methotrexate is the only one that is associated with moderate to severe toxicity. Approximately 25% of dogs and cats receiving
methotrexate, develop gastrointestinal tract signs consisting of anorexia, vomiting, or diarrhea. Anorexia and vomiting are more common than diarrhea and usually occur after the patient has been receiving the drug for more than 2 weeks. In these cases treatment with an antiemetic, such as metoclopramide, on the days the animal receives the methotrexate, at a dosage of 0.1 to 0.3 mg/kg PO every 8 hours, alleviates or eliminates the upper gastrointestinal tract signs. We also use maropitant (Cerenia, Pfizer Animal Health, Kalamazoo, Mich.) at a dosage of 2 mg/kg PO every 24 hours to prevent chemotherapy-associated nausea and vomiting. Gastroprotectants, such as famotidine (0.5-1 mg/kg PO q12-24h) may also be effective in preventing or minimizing this adverse effect. In cases of methotrexate-associated diarrhea, treatment with a bismuth subsalicylate–containing product (Pepto-Bismol) may also alleviate or eliminate the signs; however, it may be necessary to discontinue the drug. Hematologic toxicity associated with LMP therapy is minimal to nonexistent. In a very small proportion of cats (i.e., <5%) receiving chlorambucil for weeks to months, serum biochemical abnormalities consistent with cholestasis that resolve on discontinuation of the drug may develop. Tonic or tonic-clonic convulsions can rarely occur in cats receiving chlorambucil.

During this phase the patient is examined every 6 to 8 weeks, at which time a complete physical examination and a CBC are performed. As with the induction protocols, owners are instructed to monitor their pet’s activity, appetite, behavior, rectal temperature, and lymph node size. As previously discussed, over the past few years we have been instructing the owners of pets with multicentric lymphoma to closely monitor the size of the lymph nodes; when the nodes start enlarging (i.e., relapse), a fourth drug is added to the LMP protocol (usually vincristine, at a dosage of 0.5-0.75 mg/m², IV, q1-2 weeks). This usually suffices to reinduce remission and maintain it for several weeks or months.

Most animals treated with this protocol remain in remission for approximately 3 to 6 months. If a relapse occurs, reinduction of remission (as discussed next) is instituted. After remission is reinduced, animals can be treated with a modified maintenance protocol, as described in previous paragraphs.

**Reinduction of remission or rescue.** Virtually every dog and cat with lymphoma treated with induction followed by maintenance chemotherapy eventually relapses; this generally occurs 3 to 6 months after the start of induction therapy (median: approximately 4 months), but it can occur within weeks of starting the maintenance phase or years after the original diagnosis was made. At this time, reinduction of remission is indicated. In my experience, remission can be reinduced one to four additional times in most dogs with relapsing lymphoma. Reinduction of remission is usually not as successful in cats as in dogs (i.e., remission is hard to reinduce in most cats with relapsing lymphoma). Therefore the following discussion on “rescue” pertains mostly to dogs with lymphoma.

There are numerous “rescue” protocols described in the literature, and as a general rule, the practitioner may have difficulty deciding what protocol to choose. We currently use the D-MAC protocol, which consists of dexamethasone, melphalan, cytosine arabinoside, and actinomycin D as our trump card for rescue (Alvarez et al., 2006). This protocol results in >70% remission rate in dogs with relapsing lymphoma; it has a
relatively low toxicity compared with that of doxorubicin-containing protocols, and it is necessary for the owner to go the veterinarian only once every 2 weeks (instead of every week). The median duration of remission using the D-MAC protocol was 61 days (range 2 to 467 days). Previous use of doxorubicin and failure to induce remission with the induction protocol were negative prognostic factors for response to this protocol. Thrombocytopenia occurred in 56% of the dogs, neutropenia in 17%, and gastrointestinal toxicity in 22%; three of the 56 dogs required hospitalization because of toxicity. Because the long-term use of melphalan is associated with severe chronic thrombocytopenia, chlorambucil, 20 mg/m², is substituted for melphalan after four cycles. If complete or partial remissions are achieved after the administration of four to six cycles of D-MAC, the patient can be started on a maintenance protocol again.

If the response to D-MAC is poor (i.e., the disease progresses), the CHOP protocol is recommended (see Box 1). Our protocol calls for two or three cycles of CHOP once the tumor has relapsed; if CR is obtained, the patient is started on maintenance chemotherapy at the end of the second or third CHOP cycle. The maintenance protocol in these animals also includes LMP, with the possible addition of vincristine (0.5 to 0.75 mg/m² IV once weekly to every other week, alternating weeks with the chlorambucil) or cytosine arabinoside (200 to 400 mg/m² subcutaneously every other week, alternating weeks with the chlorambucil).

After a second relapse occurs, D-MAC or CHOP is administered for two additional cycles, as described in the preceding paragraph. In our experience, after the second and third relapses, the percentage of animals in which remission can be easily reinduced decreases with each subsequent cycle. This likely stems from the development of multiple-drug resistance by the tumor cells. We usually tell owners that after each subsequent relapse, the probability and duration of remission are about half of those in the previous one. Other protocols that have been successful in reinducing remission in dogs with lymphoma are listed in Box 1. Although the probability of reinducing remission is considerably lower in cats than in dogs, one of the protocols listed in Box 1 can be used for this purpose.

In cats, we have used doxorubicin- or mitoxantrone-containing protocols with some degree of success (see Box 1); asparaginase-containing protocols may also be used but generally are not as effective as in dogs.

**Intensification.** If a dog is undergoing induction therapy but only partial remission (PR) is obtained, intensification with one or two doses of L-asparaginase (10,000 to 20,000 IU/m² IM or SQ, repeated once at a 2- to 3-week interval) may be indicated. This drug can rapidly induce CR in most dogs with lymphoma that have shown only PR while receiving COP-based protocols. Asparaginase should not be used in dogs with a history of pancreatitis or in those that are at high risk for acute pancreatitis (i.e., obese, middle-age female dogs). In my experience, L-asparaginase appears to be less effective in cats than in dogs; doxorubicin (1 mg/kg IV q3 weeks) or mitoxantrone (4 to 6 mg/m² IV q3 weeks) can be used as intensifying agents in cats. In a recent study only two of thirteen (15%) cats with lymphoma treated with L-asparaginase underwent CR, and two of thirteen (15%) underwent PR; these response rates are quite a bit lower than those reported in dogs (i.e., 70%) (LeBlanc et al., 2007).
CHOP-Based Protocols

Although I do not personally use CHOP-based protocols, such as the UW-19 or UW-25, to treat dogs with multicentric lymphoma, I occasionally use them in dogs with diffuse small intestinal lymphoma. However, numerous articles on CHOP-based protocols in dogs with lymphoma have appeared in the literature in the last few years. The most attractive aspect of using CHOP-based protocols is that the patient is under treatment for a finite period (i.e., 19 weeks for the UW-19 and 25 weeks for the UW-25); when the protocol ends, the patient is closely monitored but does not receive additional chemotherapy (i.e., no maintenance). This feature is extremely important in humans undergoing chemotherapy, in whom the prevalence of adverse effects is extremely high and the patient is looking forward to a chemotherapy-free life. However, people considering chemotherapy for their pets may not share this sentiment. As a general rule, the probability and severity of toxicity with CHOP-based protocols are higher than with COP-based protocols. Box 1 lists the UW-19 protocol, commonly used by numerous oncologists.

Should You Use COP-Based or CHOP-Based Protocols?

Clinicians have been debating the relative merits of COP- and CHOP-based protocols for several years. However, because most institutions or clinicians prefer one protocol over the other, because most of the reports on COP-based protocols are 10 to 20 years old, and because in most reports of COP- or CHOP-based chemotherapy studies the endpoint has been remission times, rather than survival times, a definitive answer is not readily available.

However, in our clinic we have a similar number of patients treated with COP- and CHOP-based (UW-19) protocols; these patients are cared for by the same group of clinicians and technicians. In a retrospective study of 101 dogs with multicentric lymphoma treated with either COP-based protocols with maintenance chemotherapy (n=71) or CHOP-based protocol (UW-19, n=30) in our clinic, the probability of achieving CR or PR was similar for both protocols (92% for dogs treated with COP versus 100% for dogs treated with CHOP) (Hosoya et al., 2007). Although the median duration of remission was significantly longer in dogs treated with CHOP than in those treated with COP (174 versus 94 days), the median survival times (MST) were not statistically different between groups. The MST in dogs receiving COP was 309 days, compared with 275 days in dogs receiving the UW-19 protocol.

The prevalence of severe myelosuppression and adverse gastrointestinal effects was significantly higher in dogs receiving CHOP chemotherapy. The cost of treatment using both protocols was similar. Therefore there is no advantage of one protocol over the other one, and the clinician must make a decision based on a variety of factors (e.g., the owner’s perception, the patient’s clinical signs and other concurrent illnesses, cost).

Management of solitary and extranodal lymphomas. The clinician faces a dilemma when confronted with a dog or cat with a solitary lymphoma, regardless of whether it is nodal (i.e., stage Ia disease) or extranodal (i.e., a solitary cutaneous or oral mass). Should the mass (or lymph node) be treated in the same manner as other solitary malignancies (i.e., by wide surgical excision)? Should the patient be treated primarily with chemotherapy? Should the patient be treated with a combination of surgery,
irradiation, and chemotherapy? Unfortunately, there are no correct answers to these questions.

In my experience, seemingly solitary lymphomas become (or already are) systemic in most animals. Exceptions include some oral and some cutaneous solitary T-cell lymphomas. Although cures have been achieved through surgical excision or irradiation of solitary lymphomas, they are extremely rare. Therefore it is important not to underestimate the malignant behavior of this neoplasm by treating the patient only with a local treatment modality, such as surgery or radiotherapy. The following guidelines can be used in this subset of patients:

1. If the tumor is easily resectable (e.g., cutaneous mass, superficial lymph node, intraocular mass) and the surgical procedure does not pose a considerable risk to the patient, the mass should be resected and the animal treated with chemotherapy.

2. If the mass is difficult or impossible to resect, or if a major surgical procedure would pose an undue risk for the animal, an FNA or a needle biopsy specimen of the mass should be obtained and the animal treated with chemotherapy (with or without radiotherapy of the primary lesion).

Radiotherapy constitutes an excellent treatment modality for dogs and cats with solitary lymphomas because the tumor cells are extremely radiosensitive. Marked responses (CR or PR) are seen within hours or days of the start of such treatment. Different sources and protocols have been used in cats and dogs with lymphoma, but in general 3 to 5 Gy per fraction is delivered daily or thrice weekly for a total of six to ten fractions (total dose, 30 to 50 Gy). We have successfully used coarse fractionation radiotherapy (7 Gy once a week for 4 treatments) followed by maintenance chemotherapy (discussed later) in dogs with solitary oral T-cell lymphomas. A recent study supports a major role for radiotherapy of oral mucocutaneous lymphomas, where median survival times >2 years were obtained (Berlato et al, 2012). Special settings in which radiotherapy is beneficial include CNS lymphomas (see following paragraphs) and upper airway lymphomas that cause respiratory compromise.

Another decision the clinician must make if chemotherapy is to be used is which protocol to use and for how long. There are also no specific guidelines for this. We use a standard induction chemotherapy protocol (COP or COAP) in most cats and dogs with solitary lymphoma after they have undergone surgical excision or irradiation. After completion of the induction phase, the animals are treated with a maintenance protocol (LMP) and remission is reinduced as necessary (as in other forms of lymphoma). With some exceptions (e.g., oral T-cell lymphomas), early relapses occur in most animals treated with only maintenance chemotherapy protocols after the surgical excision of solitary lymphomas.

Central nervous system lymphoma. The treatment of choice for cats and dogs with primary or secondary epidural lymphoma is multiple-agent chemotherapy with or without radiotherapy. If radiotherapy facilities are not available, multiple-agent chemotherapy alone is an effective approach. It is my clinical impression that the surgical excision of such masses does not provide a therapeutic advantage over chemotherapy alone or radiotherapy plus chemotherapy, given the fact that the latter two forms of treatment consistently induce rapid remissions (i.e., within 12 to 36 hours of the initiation of
therapy). However, because surgery may be necessary to confirm the diagnosis, surgical excision of the mass is usually attempted at that time. If radiotherapy is available, it is quite effective. The COAP protocol alone is effective in inducing remission in cats with epidural lymphoma.

In cats and dogs with lymphoma of the neuropil (i.e., true CNS lymphoma), chemotherapy with or without radiotherapy is the preferred protocol. Intrathecal chemotherapy can be used in cats and dogs with confirmed or highly likely neuropil lymphoma. The drug of choice is cytosine arabinoside because it is almost nontoxic, it is inexpensive, and it is easy to administer. However, IV administration of this drug as a constant rate infusion (CRI) at dosages of 200 to 600 mg/m² over 24 to 72 hours achieves similar results and is our preferred approach. Responses to intrathecal or IV CRI cytosine arabinoside are usually quite spectacular. Dogs and cats that are tetraparetic, demented, or comatose usually regain normal neurologic status within 6 to 48 hours of receiving the first dose of this agent. In addition, disappearance of the neoplastic cells from the CSF occurs within hours of the injection.

We frequently induce clinical and cytologic remission (i.e., normal neurologic status and disappearance of neoplastic cells from CSF) in cats and dogs with primary or secondary CNS lymphoma treated with COAP (using cytosine arabinoside as an IV infusion). As previously discussed, an alternative drug that crosses the blood-brain barrier and is effective in eliminating lymphoma cells is lomustine (CCNU; see Box 80-1) administered at a dosage of 60 mg/m² PO every 3 weeks in dogs and at a dosage of 10 mg/cat every 3 weeks in cats; we have seen marked improvement or disappearance of neurologic signs in dogs and cats with lymphoma treated with this drug.

Despite the fact that remissions are easily attained in dogs and cats with CNS lymphoma, they are often relatively short in duration compared with disease in other anatomic locations. Most dogs and cats with CNS lymphoma relapse within 2 to 4 months of diagnosis; however, prolonged remissions (i.e., 6 to 12 months) are possible.

**Ocular lymphoma.** Ocular lymphoma can be treated using a variety of modalities. However, the eye behaves similarly to the blood-brain barrier in that adequate intraocular concentrations of chemotherapeutic agents are usually difficult to attain. If the clinician and owner want to try to preserve the animal’s eye, there are several alternatives to enucleation. As in animals with CNS lymphoma, the administration of cytosine arabinoside as a slow IV drip usually results in remission of the tumor. Lomustine is also effective in dogs and cats with intraocular lymphoma.

**Cutaneous lymphoma.** Cutaneous lymphoma is the most common extranodal form of lymphoma in dogs seen in the Midwest. In dogs with cutaneous involvement secondary to multicentric lymphoma, we use a standard chemotherapy protocol (i.e., COP or COAP). In dogs with epitheliotropic T-cell lymphomas we use either lomustine (CCNU)-containing protocols. In a study of 46 dogs with epidermotropic cutaneous T-cell lymphoma, 15 (33%) underwent CR and 23 (50%) underwent PR, for a response rate of 83%. The median number of treatments to achieve a response was 1 (range, 1-6). The overall median duration of response was 94 days (range, 22-282). Sixteen dose reductions were required because of neutropenia (10/46), thrombocytopenia (1/46), anemia (1/46), increased liver enzyme activity (3/46), or unspecified reasons (1/46). As
discussed above, radiotherapy is effective in localized cutaneous/mucocutaneous T-cell lymphomas.

**Alimentary lymphoma.** We use standard chemotherapy protocols (i.e., COP or COAP) in dogs and cats with solitary mural or nodal (e.g., mesenteric or ileoceccolic lymph node) involvement. Even though surgery is not necessarily indicated for these dogs and cats, a fair number are referred after exploratory surgery and an incisional or excisional biopsy has been performed. In general, the response in these animals is good. Dogs and cats with diffuse intestinal lymphoma usually respond poorly to chemotherapy. Responses to doxorubicin-containing protocols (i.e., CHOP) appear to be better than those to COAP, although survival times are short (4 to 6 months). Dogs with colorectal lymphoma and cats with gastric lymphoma tend to respond extremely well to COP-based chemotherapy; we have documented remission times >3 years in these subsets of patients. In cats this may be related to the fact that *Helicobacter* spp. may play a role in the development of gastric lymphoma, as *H. pilori* does in people; we treat all cats with gastric lymphoma with combination chemotherapy and antibiotics proven effective in cats with *Helicobacter* infection.

In cats with epitheliotropic intestinal lymphoma, a common, small lymphocytic form of the disease in older individuals, we have used a very conservative approach with excellent results. We administer a combination of chlorambucil (20 mg/m², PO q2 weeks) plus prednisone (1-2 mg/kg, PO q24-48h) or dexamethasone (4 mg/cat, PO q1-2 weeks); if clinical signs do not improve within 3 or 4 weeks, we add vincristine (0.5 mg/m², IV, q1-2 weeks). Most cats treated with this protocol have marked improvement of the clinical signs and typically gain weight. Interestingly, some of the cats exhibit no appreciable decrease in mesenteric lymph node size, despite the remarkable clinical improvement. For these cats I use the approach of “treating the patient, not the disease” (i.e., as long as the patient feels well and is free of clinical signs, the current treatment is continued).

**“Low-Budget” Lymphoma Protocols**

Quite frequently, the clinician is evaluating a dog or cat with lymphoma that should benefit from chemotherapy, but because of finances or other issues (e.g., time commitment) the owners are not interested in the standard multiagent chemotherapy approach. Because most of these patients are asymptomatic, they would benefit from some form of therapy. In our clinic we have used one of the following quite successfully: prednisone alone, prednisone and chlorambucil, chlorambucil alone, lomustine alone, or prednisone and lomustine. Although the duration of remission is shorter than when using COP-based protocols, most of these patients (and their owners) enjoy prolonged (i.e., months), good-quality survival times. These protocols are listed in Box 1.
Suggested Readings


Shelton GH et al: Feline immunodeficiency virus and feline leukemia virus infection and their relationships to lymphoid malignancies in cats: a retrospective study, J AIDS
## Box 1 Chemotherapy Protocols I Use To Treat Dogs and Cats with Lymphoma

### 1. Induction of Remission
#### a. COP protocol
Cyclophosphamide: 50 mg/m² BSA, PO, q48h; or 300 mg/m² BSA, PO, every 3 weeks (dogs or cats)\
Vincristine: 0.5 mg/m² BSA, IV, once a week\
Prednisone: 40-50 mg/m² BSA, PO, q24h for a week; then 20-25 mg/m² BSA, PO, every other day.

#### b. UW-19 protocol (This protocol uses no maintenance chemotherapy—for additional information see text)
Week 1: Vincristine 0.5-0.75 mg/m², IV
Asparaginase 400 IU/KG IM or SC
Prednisone 2 mg/kg PO q24h
Week 2: Cyclophosphamide 200-250 mg/m², IV
Prednisone 1.5 mg/kg PO q24h
Week 3: Vincristine 0.5-0.75 mg/m², IV
Prednisone 1 mg/kg PO q24h
Week 4: Doxorubicin 30 mg/m² (or 1 mg/kg if $\leq$ 10 kg) IV
Prednisone 0.5 mg/kg PO q24h
Week 5: **No treatment**
Week 6: Vincristine 0.5-0.75 mg/m², IV
Week 7: Cyclophosphamide 200-250 mg/m², IV
Week 8: Vincristine 0.5-0.75 mg/m², IV
Week 9: Doxorubicin 30 mg/m² (or 1 mg/kg if $\leq$ 10 kg) IV
Week 10: **No treatment**
Week 11: Vincristine 0.5-0.75 mg/m², IV
Week 12: Cyclophosphamide 200-250 mg/m², IV
Week 13: Vincristine 0.5-0.75 mg/m², IV
Week 14: Doxorubicin 30 mg/m² (or 1 mg/kg if $\leq$ 10 kg) IV
Week 15: **No treatment**
Week 16: Vincristine 0.5-0.75 mg/m², IV
Week 17: Cyclophosphamide 200-250 mg/m², IV
Week 18: Vincristine 0.5-0.75 mg/m², IV
Week 19: Doxorubicin 30 mg/m² (or 1 mg/kg if $\leq$ 10 kg) IV

### 2. Intensification
**Dogs**
L-Asparaginase: 10,000-20,000 IU/m² IM (one or two doses)
or
Vincristine: 0.5-0.75 mg/m² IV q1-2 weeks

**Cats**
Doxorubicin: 1 mg/kg IV q3 weeks
or
Mitoxantrone: 4-6 mg/m² IV q3 weeks

### 3. Maintenance‡
#### a. LMP protocol
Chlorambucil: 20 mg/m² PO q2 weeks

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‡ Additional information for LMP protocol can be found in the text.
Methotrexate: 2.5 mg/m² PO two or three times per week
Prednisone: 20 mg/m² PO q48h

b. COAP protocol
Use as above every other week for six treatments, then every third week for six additional treatments, then try to maintain the animal on one treatment every fourth week. Maintenance therapy is continued until the tumor relapses.

4. Rescue

Dogs
a. D-MAC protocol (14-day cycle)
Dexamethasone: 0.5 mg/lb (1 mg/kg) PO or SC on days 1 and 8
Actinomycin D: 0.75 mg/m² as IV push on day 1
Cytosine arabinoside: 200-300 mg/m² as IV drip over 4 hours or SC on day 1
Melphalan: 20 mg/m² PO on day 8§
b. AC protocol (21-day cycle)
Doxorubicin: 30 mg/m² (or 1 mg/kg for dogs under 10 kg) IV on day 1
Cyclophosphamide: 100-150 mg/m² PO on days 15 and 16
c. CHOP protocol (21-day cycle)
Cyclophosphamide: 200-300 mg/m² PO on day 10
Doxorubicin: 30 mg/m² (or 1 mg/kg for dogs under 10 kg) IV on day 1
Vincristine: 0.75 mg/m² IV on days 8 and 15
Prednisone: 20-25 mg/m² PO q48h

Cats
a. ACD protocol (21-day cycle)
Doxorubicin: 1 mg/kg IV on day 1
Cyclophosphamide: 200-300 mg/m² PO on day 10 or 11
Dexamethasone (4 mg/cat q1-2 weeks can be added to this protocol)
b. MiCD protocol (21-day cycle)
Mitoxantrone: 4-6 mg/m² as IV drip over 4-6 hours on day 1
Cyclophosphamide: 200-300 mg/m² PO on day 10 or 11
Dexamethasone (4 mg/cat q1-2 weeks can be added to this protocol)
c. MiCA protocol (21-day cycle)
Mitoxantrone: 4-6 mg/m² in IV drip over 4-6 hours on day 1
Cyclophosphamide: 200-300 mg/m² PO on day 10 or 11
Cytosine arabinoside: 200 mg/m² in IV drip over 4-6 hours (mixed in the same bag with mitoxantrone) on day 1
Dexamethasone (4 mg/cat q1-2 wks can be added to this protocol)

5. “Low-Budget” Protocols
Prednisone: 50 mg/m² PO q24h for 1 week; then 25 mg/m² PO q48h
Chlorambucil: 20 mg/m² PO q2 weeks
Lomustine: 60 mg/m² PO q3 weeks in dogs; 10 mg (total dose) q3 weeks in cats
Prednisone and chlorambucil: doses as above
Prednisone and lomustine: doses as above

PO, By mouth; IV, intravenous; SC, subcutaneous; BSA, body surface area; IM, intramuscular.
*Unless otherwise specified, protocols can be used in both dogs and cats.
†Use for 6-10 weeks, then use LMP.
‡Use until relapse occurs, then go to "rescue."
§After four doses, substitute chlorambucil (20 mg/m² PO q2 weeks) for melphalan.
||The duration of chemotherapy using this protocol is variable.