LYMPHOMA IN THE DOG: COP, CHOP OR SOMETHING ELSE?  

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Once a cytologic or histopathologic diagnosis of lymphoma is established, the prognosis and potential therapeutic options should be discussed with the pet’s owner. 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 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. Most dogs with lymphoma treated in a similar fashion 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 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 weeks to months after diagnosis. Therefore, the mainstay of treatment for animals with lymphoma is chemotherapy, given the fact that lymphomas are (or will be) systemic neoplasms. Surgery or radiotherapy, or both, can be used to treat localized lymphomas before or during chemotherapy. General guidelines for the management of patients with lymphoma are presented here. The protocols I recommend have been used at our clinic with a success rate comparable to those of other treatments published in the literature.

The treatment of dogs with lymphoma is divided into several phases, or strategies: induction of remission, intensification, maintenance, and reinduction of remission or “rescue” (see Table 1). Immediately after diagnosis, a relatively aggressive multiple-agent chemotherapy protocol (cyclophosphamide, vincristine [Oncovin], cytosine arabinoside, prednisone [COAP]) is used to induce remission. During this phase, which lasts 8 weeks, the dogs are evaluated weekly by a veterinarian, at which time they receive an 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 animal requires less intensive monitoring (once every 6 to 8 weeks). This phase continues until the tumor relapses, 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 (at OSU we typically use the LMP protocol for routine maintenance, but we substitute Cytosar for the methotrexate at a dosage of 200 to 300 mg/m² subcutaneously [SQ] every other week when maintenance is induced for a second time). If at the end of the induction phase the patient is not in CR, it is recommended 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.

**Induction of Remission**

My protocol of choice for the induction of remission is COAP. The agents in this protocol consist of cyclophosphamide (Cytoxan), vincristine (Oncovin), cytosine arabinoside (Cytosar-U), and prednisone; these four drugs are also currently available as generic products, belong to four different categories, have different mechanisms of action, and do not have superimposed toxicities (with the exception of cyclophosphamide and cytosine arabinoside, which are myelosuppressive; but the latter is used only for a short period); thus they fulfill the basic criteria of multiple-agent chemotherapy. The cytosine arabinoside is usually administered by the subcutaneous (SQ) route, because given its short half-life and S-phase-specific mechanism of action, an IV bolus injection results in minimal cell kill; SQ 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 8 weeks, and weekly visits to the veterinarian are necessary during this time.

During the induction phase, toxicity is minimal (less than 15% to 20%) 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); the neutrophil nadir usually occurs around day 7 or 8, which is explained by the fact that two myelosuppressive agents are given during the initial 2 to 4 days of treatment. In most cases the neutropenia is mild (2,000 to 3,500 cells/µl). The neutropenia is severe if the animal has neoplastic bone marrow infiltration before the
initiation of treatment, or receives the cytosine arabinoside by constant-rate IV infusion, rather than SQ. Gastrointestinal toxicity is minimal to nonexistent. 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, to measure its lymph nodes (if superficial lymphadenopathy was present initially), and to take the pet’s rectal temperature daily (pyrexia is usually secondary to neutropenia and sepsis). If pyrexia develops, owners are instructed to contact their veterinarian so that the pet can undergo a complete physical examination and CBC. Treatment with COAP results in CR within 1 to 14 days of the start of therapy in most animals (more than 85% in dogs and 70 to 75% in cats). This remission is usually maintained throughout the induction phase.

In dogs with diffuse alimentary lymphoma and those with mycosis fungoides or mucocutaneous lymphoma, we use a more aggressive doxorubicin-containing protocol (CHOP; see Table 1), because in my experience, the response rate to COAP is low. This protocol is more expensive and is more likely to cause adverse effects than the COAP protocol. We have recently seen encouraging responses to lomustine (CCNU) in a limited number of dogs with epidermotropic and other types of T-cell lymphoma (see Table 1).

In dogs 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 mg/m² as an IV infusion over 24 hours for 1 to 4 days) in an attempt to increase the concentration of this drug in the CNS.

**Maintenance**

The protocol recommended for the maintenance phase of treatment is LMP (“lump”), which consists of chlorambucil (Leukeran), methotrexate, and prednisone. These three drugs also act by three different mechanisms of action, have different toxicities, and have proved effective as single agents in cats and dogs with lymphoma. The advantages of this protocol include its reduced cost, as 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.

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. In approximately 25% of dogs and cats receiving methotrexate, gastrointestinal tract signs consisting of anorexia, vomiting, or diarrhea develop. 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 (Reglan) on the days the animal receives the methotrexate, at a dosage of 0.1 to 0.3 mg/kg PO q8h, alleviates or eliminates the upper gastrointestinal tract signs. In cases of methotrexate-associated diarrhea, treatment with a bismuth subsalicylate–containing product (e.g., 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.

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.

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

**Reinduction of Remission or Rescue**

Virtually every dog with lymphoma treated with maintenance chemotherapy eventually relapses; this generally occurs 6 to 8 months after the start of induction therapy, 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 our 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 cannot be reinduced 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 which protocol to choose. For example, if a dog is being treated with the LMP maintenance protocol and the tumor starts to relapse (i.e.; either the owner or the clinician notices that the lymph nodes are just enlarging), we typically add vincristine (0.5 mg/m², IV, q2weeks) on the weeks the patient is not receiving the chlorambucil; if tumor growth is arrested, but remission is not obtained, we increase the dose of vincristine to 0.75 mg/m² q2weeks. This intervention alone frequently results in a long-lasting remission. If the patient is examined when the tumor has progressed to an advanced stage, we usually recommend administering l-asparaginase, as described in Table 1.

We currently use the D-MAC protocol (see Table 1), consisting of dexamethasone, melphalan (Alkeran), cytosine arabinoside (Cytosar-U), and actinomycin D (Cosmegen), as our “trump card” for rescue. This protocol results in an approximately 80% remission rate in dogs with relapsing lymphoma treated at our clinic; it has a relatively low toxicity, as 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). Because the long-term use of melphalan is associated with moderate-to-severe chronic thrombocytopenia, chlorambucil (20 mg/m²; Leukeran) 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), we recommend using the ADIC or CHOP protocols (see Table 1). Our protocol calls for two or three cycles of ADIC or CHOP once the cancer has relapsed; if CR is obtained, the patient is started on maintenance chemotherapy at the end of the second or third ADIC or 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 Leukeran) or cytosine arabinoside (200 to 400 mg/m² SQ every other week, alternating weeks with the Leukeran).

After a second relapse occurs, D-MAC, ADIC, 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.

**Intensification**

If a dog is undergoing induction therapy but only partial remission (PR) is obtained, intensification with one or two doses of l-asparaginase (Elspar) (10,000 to 20,000 IU/m² IM 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 COAP. 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).

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

We have been asking ourselves this question 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, this information was 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. We recently published the results of 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 (Hosoya et al.). The probability of achieving complete or partial remission was similar for both protocols (92% for dogs treated with COP versus 100% for dogs treated with CHOP). 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 to 275 days in dogs receiving the UW-19 protocol. The MST was similar for dogs with B- or T-cell lymphoma treated with the COP-based protocols (321 versus 378 days, respectively); there were not enough dogs with T-cell phenotype treated with the UW-19 to perform statistical analysis.
The prevalence of severe myelosuppression and GI adverse 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, and the clinician must make a decision based on a variety of factors (e.g.; owners’ perception, patient’s clinical signs and other concurrent illnesses, cost, etc).

Table 1. Chemotherapy Protocols Used to Treat Dogs and Cats* with Lymphoma at The Ohio State University Veterinary Teaching Hospital

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Induction of remission</th>
<th>Intensification</th>
<th>Maintenance</th>
<th>Rescue</th>
</tr>
</thead>
<tbody>
<tr>
<td>COAP</td>
<td>Cyclophosphamide (Cytoxan): 50 mg/m^2 PO q48h in dogs or 200-300 mg/m^2 PO q3weeks in cats</td>
<td>Vincristine (Oncovin): 0.5 mg/m^2 IV once a week</td>
<td>Cytosine arabinoside (Cytosar-U): 100 mg/m^2 daily as an IV drip or SQ for only 2 days in cats and 4 days in dogs</td>
<td>Prednisone: 50 mg/m^2 PO q24h for a week, then 20 mg/m^2 PO q48h</td>
</tr>
<tr>
<td>DOGS</td>
<td>l-asparaginase (Elspar): 10,000-20,000 IU/m^2 IM (one or two doses)</td>
<td>or Vincristine (Oncovin): 0.5-0.75 mg/m^2 IV every 1 to 2 weeks.</td>
<td></td>
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</tr>
<tr>
<td>CATS</td>
<td>Doxorubicin (Adriamycin): 1 mg/kg IV every 3 weeks</td>
<td>or Mitoxantrone (Novantrone): 4-6 mg/m^2 IV every 3 weeks</td>
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</tbody>
</table>

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<tbody>
<tr>
<td>LMP</td>
<td>Chlorambucil (Leukeran): 20 mg/m^2 PO q2weeks</td>
<td>Methotrexate (Methotrexate): 2.5 mg/m^2 PO 2 to 3 times per week</td>
<td>Prednisone: 20 mg/m^2 PO q48h</td>
<td></td>
</tr>
<tr>
<td>COAP</td>
<td>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.</td>
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4. Rescue

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>D-MAC</td>
<td>Dexamethasone: 0.5 mg/lb (0.23 mg/kg) PO or SQ on days 1 and 8</td>
<td>Actinomycin D (Cosmegen): 0.75 mg/m^2 as IV push on day 1</td>
<td>Cytosine arabinoside (Cytosar): 200-300 mg/m^2 as IV drip over 4 hours or SQ on day 1</td>
<td>Melphalan (Alkeran): 20 mg/m^2 PO on day 8§</td>
</tr>
<tr>
<td>AC</td>
<td>Doxorubicin (Adriamycin): 30 mg/m^2 (or 1 mg/kg for dogs under 10 kg) IV on day 1</td>
<td>Cyclophosphamide (Cytoxan): 100-150 mg/m^2 PO on days 15 and 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>Cyclophosphamide (Cytoxan): 100-150 mg/m^2 IV on day 1</td>
<td>Doxorubicin (Adriamycin): 30 mg/m^2 (or 1 mg/kg for dogs under 10 kg) IV on day 1</td>
<td>Vincristine (Oncovin): 0.75 mg/m^2 IV on days 8 and 15</td>
<td>Prednisone: 20-25 mg/m^2 PO q48h</td>
</tr>
<tr>
<td>CATS</td>
<td>Mitoxantrone (Novantrone): 4-6 mg/m^2 as IV drip over 4-6 hours on day 1</td>
<td>Cyclophosphamide (Cytoxan): 200-300 mg/m^2 PO on day 15 or 16</td>
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MiCA protocol (21-day cycle)
- Mitoxantrone (Novantrone): 4-6 mg/m² in IV drip over 4-6 hours on day 1
- Cyclophosphamide (Cytoxan): 200-300 mg/m² PO on day 15 or 16
- Cytosine arabinoside (Cytosar-U): 200 mg/m² in IV drip over 4-6 hours (mixed in the same bag with mitoxantrone) on day 1

CHOP protocol (21-day cycle)
- Cyclophosphamide (Cytoxan): 200-300 mg/m² PO on day 10
- Doxorubicin (Adriamycin): 1 mg/kg IV on day 1
- Vincristine (Oncovin): 0.5 mg/m² IV on days 8 and 15
- Prednisone: 20-25 mg/m² PO q48h

5. “Low-budget” protocols
- Prednisone: 50 mg/m², PO, q24h for 1 week; then 25 mg/m², PO, q48h
- Chlorambucil (Leukeran): 20 mg/m², PO, q2weeks
- Lomustine (CCNU; Ceenu): 60-90 mg/m², PO, q3weeks in dogs; 10 mg (total dose) q3weeks in cats
- Prednisone and chlorambucil: doses as above
- Prednisone and lomustine: doses as above

*Unless otherwise specified, protocols can be used in both dogs and cats.
†Use for 6 to 10 weeks, then use LMP.
‡Use until relapse occurs, then go to “rescue.”
§After four doses, substitute Leukeran (20 mg/m², PO, q2 wk) for Alkeran.