Canine Lymphomas (Part 2):
Choosing the Right Chemotherapy Protocol for Your Patients
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Canine lymphomas represent a diverse group of cancers whose clinical behavior ranges from indolent and relatively benign to rapidly progressive and life-threatening. The majority of lymphomas in dogs are multicentric in nature, primarily involving peripheral lymph nodes, with secondary involvement of the liver, spleen, bone marrow, and other organs. Multicentric lymphomas are typically widely disseminated at the time of diagnosis, and, as such, require treatment with systemic chemotherapy. Rarely, lymphomas may occur as solitary tumors localized to a single anatomic site; in these cases surgery and/or radiation therapy may be sufficient to effect durable tumor control. This session will review the variety of therapies available for canine lymphomas, with special focus on chemotherapy protocols for the treatment of multicentric lymphomas.

Chemotherapy for multicentric lymphomas

Multicentric lymphomas represent approximately 80% of all lymphomas in the dog. They typically present with locoregional or generalized lymphadenomegaly. Approximately 70-90% of canine multicentric lymphomas are intermediate-to-high grade in nature, meaning that they progress rapidly and become life-threatening in short order without treatment. The remaining 10-30% of multicentric lymphomas are low-grade cancers. These cancers progress slowly and insidiously, and are only rarely life-threatening. The recommended therapies for low-grade and intermediate-to-high grade lymphomas therefore differ significantly.

The therapy of low-grade lymphomas is controversial, and a standard-of-care therapy has not been established. The goal of therapy for low grade lymphomas is to minimize cancer progression and maintain quality of life. Due to their indolent nature, many oncologists question whether these cancers even require treatment at all. When treatment is elected, typical treatment protocols include single-agent prednisone therapy or combined oral prednisone and chlorambucil. A commonly used protocol includes chlorambucil dosed at 0.2 mg/kg PO q 24 hrs for 7-14 days, followed by dosing at 0.1 mg/kg PO q 24 hrs indefinitely. Prednisone is dosed at 1 mg/kg PO q 24 hrs for 7-14 days, followed by 0.5 mg/kg PO q 24 hrs indefinitely. Survival times for dogs with low-grade lymphomas are typically long, with one recent report documenting a median survival time of 4.4 years in 75 dogs with low-grade lymphomas.

The therapy of intermediate-to-high grade multicentric lymphomas is more aggressive than that for low-grade lymphomas. The goal of chemotherapy of these cancers is to induce complete cancer remission; that is, to render the cancer clinically undetectable. It should be noted that complete remission is not tantamount to cure. Most of these lymphomas will eventually relapse following initial remission, and relapsed lymphoma is usually fatal. A small proportion (less than 5%) of dogs with intermediate-to-high grade lymphomas is apparently cured by chemotherapy. In general, combination chemotherapy protocols incorporating several drugs with activity against lymphoma are needed to effect durable remissions of intermediate-to-high grade tumors, and cure is essentially impossible with single-agent chemotherapy. Several commonly used treatment protocols are discussed below.

CHOP

The most effective chemotherapy protocols for treating intermediate-to-high grade multicentric lymphomas combine cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin™), and prednisone. L-asparaginase is also commonly added to CHOP protocols, although the addition of this drug does not appear to extend remission duration or survival time. Several permutations of the CHOP protocol are described in the veterinary literature, including UW-25, UW-19, VELCAP, ACOPA, etc. None of these protocols is demonstrably superior to the others, and all afford similar rates of complete remission (approximately 70-90%), median first remission duration (approximately 7-9 months), and median survival time (approximately 1 year). CHOP protocols are considered the standard-of-care treatment for intermediate-to-high grade multicentric lymphomas. The major advantages of CHOP include high remission rates and superior first remission duration and survival time when compared to other protocols. The major disadvantages of CHOP are its intensity (frequent and numerous treatments), expense, and relatively higher potential for side effects compared to other protocols. It should be noted, however, that only 5-10% of treated dogs will experience serious side effects which require hospitalized care. Common side effects include neutropenia, thrombocytopenia, vomiting, diarrhea, loss of appetite, and, in some dogs, alopecia.

Single-agent doxorubicin

Doxorubicin (Adriamycin™) is the single most effective drug for the treatment of intermediate-to-high grade lymphomas, and it is the only drug capable of inducing durable lymphoma remission when given as a single agent. It induces cancer remission in 60-80% of patients, affording median first remission durations of approximately 4-5 months. Dogs treated with single-agent doxorubicin typically live 7-9 months following diagnosis. Doxorubicin is given at a dose of 30 mg/m² (1 mg/kg in dogs weighing less than 15 kg)
intravenously (IV) once every 2-3 weeks for a total of five doses. The lifetime dose for any dog is capped at 150 mg/m² in order to avoid cumulative cardiotoxicity. Single-agent doxorubicin is an excellent alternative to CHOP in that it involves fewer treatments given over a shorter time span, and is significantly less expensive. Side effects of doxorubicin, in addition to those listed above for CHOP, include cardiotoxicity and extravasation injury. Acute cardiac toxicity is often manifested by arrhythmias, which are usually subclinical, but in very rare instances may be serious or fatal. Repeated doxorubicin dosing causes cumulative injury to the myocardium, resulting in a condition very similar to dilated cardiomyopathy. Doxorubicin cardiomyopathy is usually refractory to positive inotropes and is very challenging to manage, thus it should be avoided at all costs. The best way to avoid cumulative cardiotoxicity is to cap a dog’s lifetime dose at 150 mg/m². Dogs with pre-existing ventricular arrhythmias, cardiomyopathy, or congestive heart failure should not be treated with doxorubicin. Heart murmurs or cardiac valvular disease by themselves are not absolute contraindications for doxorubicin therapy so long as congestive heart failure is not present. Doxorubicin must be given through an IV catheter which is perfectly placed on the first attempt. Extravasation of doxorubicin into the perivascular tissues due to improper catheter placement will lead to severe tissue necrosis.

COP
Protocols combining cyclophosphamide, vincristine (Oncovin™), and prednisone were among the first combination chemotherapy protocols devised for the treatment of canine lymphomas. COP induces complete remission in 55-75% of canine lymphoma patients, and affords median remission durations of 4-6 months; thus, the clinical efficacy of COP is similar to that of single-agent doxorubicin. An advantage of COP over doxorubicin is its relatively lower expense, particularly if cyclophosphamide is dosed orally rather than intravenously. A recent study confirmed that total exposure to the active metabolite of cyclophosphamide (4-hydroxycyclophosphamide) is equivalent in dogs dosed via either the oral or intravenous routes. COP is also generally associated with fewer side effects than doxorubicin. A major disadvantage to COP is that there is no defined end point to the protocol – chemotherapy is essentially administered indefinitely, until it is observed to no longer be effective (i.e. the lymphoma comes out of remission in spite of continued chemotherapy). This tends to negate the cost savings of COP relative to single-agent doxorubicin over time. As with CHOP, several permutations of COP exist. The author uses a protocol in which vincristine is dosed at 0.7 mg/m² IV once weekly for four consecutive weeks, cyclophosphamide dosed at 250-300 mg/m² PO, divided over days 4-6 following each vincristine treatment, and prednisone is dosed at 1 mg/kg PO q 24 hrs continuously during these four weeks. If complete cancer remission is present after 4 weeks, vincristine and cyclophosphamide are administered once every 3 weeks, and prednisone is continued at 1 mg/kg PO q 48 hrs. This is continued indefinitely until cancer relapse occurs.

Lomustine (CCNU)-based protocols
Lomustine is a useful drug for the treatment of canine lymphomas because of its relatively low expense, and its convenient route and schedule of administration (orally, once every 3 weeks). While typically used in rescue chemotherapy protocols for relapsed lymphoma, lomustine can be given as front-line therapy as well. It should be noted that response data for dogs treated with lomustine for non-relapsed lymphoma are generally lacking in the veterinary literature. Single-agent lomustine induces cancer remission in 27% of dogs with relapsed lymphoma, and median remission duration is approximately 3 months. Combined lomustine/prednisone achieves complete remission in 35% of dogs with untreated lymphoma, and affords a median remission duration of approximately 1.5 months. A newer protocol combining lomustine, L-asparaginase, and prednisone (LAP) in dogs with relapsed lymphoma affords an improved remission rate (70-80%), but not a substantially longer remission duration (about 2.5 months) relative to single-agent lomustine or lomustine/prednisone. Hepatotoxicity is a major limitation of lomustine chemotherapy. Although the true incidence of hepatotoxicity is unknown, increased serum ALT activity occurs in up to 84% of dogs receiving lomustine. Fortunately, the incidence of functionally significant hepatopathy appears to be much lower (approximately 1-6% of treated dogs). Coadministration of the nutraceutical Denamarin® (Nutramax Laboratories, Inc.) was recently shown to reduce the frequency and severity of increased serum ALT activity in lomustine-treated dogs, and many veterinary oncologists accept coadministration of Denamarin as the standard-of-care. Denamarin is relatively expensive, particularly for large dogs, and its expense tends to offset the cost savings of lomustine-based protocols relative to other chemotherapy protocols.

Single-agent prednisone
Prednisone is a popular treatment for lymphoma due to its minimal expense and excellent safety profile. Prednisone is reported to induce cancer remission in 20-40% of dogs with lymphoma. Such remissions are usually short, lasting an average of 1-2 months. Prednisone also improves appetite and reduces clinical signs of malaise in many dogs with lymphoma. However, a recent study showed that single-agent prednisone did not afford a survival benefit to dogs with lymphoma relative to dogs receiving no therapy at all. Furthermore, owners electing to treat their dog’s lymphoma with single-agent prednisone should be advised that such treatment may foster the emergence of multidrug resistance, rendering the cancer more refractory to future attempts at chemotherapy.
Chemotherapy of non-multicentric (extranodal) lymphomas

Extranodal lymphomas are significantly less common than nodal lymphomas in dogs, and as such, less is known about optimal therapy for these tumors. Common extranodal forms of lymphoma include cutaneous, mediastinal, and gastrointestinal lymphomas. Most extranodal lymphomas are T-cell lymphomas, which tend to respond more poorly to chemotherapy than B-cell lymphomas. CHOP may be employed as first-line therapy for extranodal lymphomas, although whether it is an optimal treatment for these cancers is controversial. Recent evidence suggests that T-cell lymphomas respond more favorably to protocols incorporating alkylating agents, such as lomustine, mechloretamine, and procarbazine. An example of this is the use of lomustine for the treatment of cutaneous lymphoma (epitheliotropic T-cell lymphoma). Lomustine, administered with or without prednisone, induces complete or partial remission in approximately 80% of dogs with cutaneous lymphoma, and is considered to be the treatment of choice for this type of lymphoma. The duration of remission is typically short (median 3.5 months), although the author has observed complete remissions lasting greater than one year in some dogs. Further investigation is required to determine whether lomustine-based protocols, or protocols based upon other alkylating agents, are superior to CHOP for the treatment of other extranodal lymphomas in dogs.

Treatment of solitary site lymphomas

Most canine lymphomas have disseminated to several organs by the time of diagnosis. However, in rare instances, lymphoma may be diagnosed at a solitary site with no apparent involvement of regional or distant organs. The optimal treatment for solitary site lymphomas is poorly defined. For tumors that are truly solitary, aggressive local therapy, such as surgery and/or radiation therapy, may be curative. The author strongly recommends thorough staging (complete blood count, serum biochemistry panel, thoracic/abdominal imaging, bone marrow aspirate) to rule out presence of metastasis prior to embarking on aggressive local therapy for any solitary site lymphoma. Histopathologic evaluation of a good-quality biopsy sample is also strongly recommended to confirm the immunophenotype (B-cell or T-cell), grade, and histologic subtype of the tumor. Some localized lymphomas (such as marginal zone B-cell lymphoma of the spleen) are readily curable with local therapy. More aggressive tumors (such as diffuse large B-cell lymphoma), even if apparently confined to a solitary site, are highly likely to spread to other organs. Patients with such tumors would likely benefit from chemotherapy in addition to aggressive local therapy.

References