Predictors of long-term survival in dogs with high-grade multicentric lymphoma

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Objective—To determine factors predicting survival in dogs with high-grade multicentric lymphoma.

Design—Retrospective cohort study.

Animals—127 dogs with high-grade multicentric lymphoma evaluated at 4 veterinary hospitals from 2000 to 2009.

Procedures—Records were reviewed to identify dogs with completely staged high-grade multicentric lymphoma treated with chemotherapy. Data collected included signalment, history, hematologic findings, tumor characteristics, treatment, and outcome. Long-term survival was defined as surviving > 2 years after diagnosis. Variables were analyzed for associations with dogs living > 2 years.

Results—Among the 127 enrolled dogs, 13 (10%) survived > 2 years with a median survival time of 914 days (range, 740 to 2,058 days). Survival rates at 3, 4, and 5 years were 4%, 3%, and 1%, respectively. At diagnosis, 11 of the 13 long-term survivors had a body weight ≥ 10 kg, PCV ≥ 35%, absence of ionized hypercalcemia, centroblastic lymphoma, immunophenotype B, absence of bone marrow involvement, and lymphoma stages I through IV and were not previously treated with corticosteroids. The same combination of factors was present in 26 of 114 (23%) dogs surviving ≤ 2 years, yielding a negative predictive value of 97.8% for long-term survivors. Four of the 6 long-term survivors that died during the study died of another cancer; 3 of them had osteosarcoma.

Conclusions and Clinical Relevance—Absence of the aforementioned combination of variables at diagnosis may help identify dogs with lymphoma that will not survive > 2 years. Other types of neoplasia, in particular osteosarcoma, may develop in long-term–surviving dogs. (J Am Vet Med Assoc 2011;238:480-485)

In human medicine, cancer survivors are defined as patients living for 5 years or longer after diagnosis. Advances in diagnostic tools and progress of chemotherapeutic strategies during the past decades have resulted in remarkable increases in survival rates for many people with chemoresponsive cancers including, among others, testicular cancer, ovarian germ cell tumors, high-grade non-Hodgkin's lymphoma, and Hodgkin’s lymphoma. Although survival rates are increasing, surviving patients may experience many health challenges and treatment-induced complications, often caused by alkylating chemotherapeutic drugs, such as the induction of second malignancies.

Lymphoma is the most common hematopoietic tumor in dogs, and its incidence is rising, probably because of improved diagnostic procedures and treatments, aging of the pet dog population, and exposure to environmental risk factors. In dogs, lymphomas are cytologically grouped into 2 main categories with different incidence rates and biological behavior. Low-grade lymphomas, which are less common, are characterized by a slow growth rate and indolent biological behavior. High-grade lymphomas are biologically aggressive and typically fatal within a few weeks when appropriate treatments are not instituted. Distinction of lymphoma on the basis of immunophenotype has also gained interest among clinicians because it appears to correspond with prognosis. In fact, B-cell and

### Abbreviations

<table>
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<th>Abbreviation</th>
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<tr>
<td>CHOP</td>
<td>Cyclophosphamide, doxorubicin, vincristine, and prednisone</td>
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<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<td>OR</td>
<td>Odds ratio</td>
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T-cell high-grade lymphomas typically have divergent patterns of sensitivity to chemotherapy, with B-cell malignancies being more chemosensitive, thereby yielding better results when chemotherapy is attempted. Multiagent chemotherapy, which incorporates drugs such as L-asparaginase, vincristine, cyclophosphamide, and doxorubicin, with or without prednisone, is the treatment of choice for high-grade lymphomas. Such protocols have resulted in complete remission rates of 60% to 90% and median survival times of 6 to 12 months.

Despite the high frequency of response to multiagent chemotherapy, curative treatment remains elusive for most dogs with high-grade multicentric lymphoma. In particular, dogs with similar signalment, stage and substage of disease, immunophenotype, and tumor anatomic location may respond differently to the same chemotherapeutic protocol. This phenomenon is partly attributable to the biology of the malignant cells, which undergo major genetic and epigenetic changes during their growth and proliferation. As a consequence of these rearrangements, natural history and response to chemotherapy may vary among animals. In addition, pharmacogenetic factors as well as tumor microenvironment may influence the response of tumor cells to treatment.

Although many data have been published on the outcome of chemotherapy in dogs with high-grade multicentric lymphoma, to the authors’ knowledge there are no reports specifically focused on long-term survivors, such as dogs living beyond 2 years after diagnosis. Most dogs with lymphoma have a life expectancy of < 1 to 1.5 years, and < 10% survive longer than 2 years. The precise characterization of the dogs that survive > 2 years would be useful in practice and in the design of future clinical trials. Indeed, identification of these dogs may help in the selection of treatments specific to the individual dog and its disease characteristics. In addition, owners may be more willing to treat their dogs if a long survival can be anticipated at diagnosis. The aim of the study reported here was to determine the proportion of dogs with high-grade multicentric lymphoma living beyond 2 years after diagnosis and to identify clinical, biological, and treatment characteristics associated with survival > 2 years.

**Materials and Methods**

Dogs—Medical records were reviewed to identify dogs with high-grade multicentric lymphoma evaluated at the authors’ veterinary hospitals during a 9-year period (2000 to 2009). Similarly diseased dogs from a previous study were also enrolled. Dogs were eligible for inclusion if they were naïve to chemotherapy when first evaluated and if they received at least 1 dose of chemotherapy afterward. Administration of corticosteroids prior to diagnosis was not considered an exclusion criterion. Dogs euthanized at the time of diagnosis were excluded.

Diagnosis of lymphoma was established on the basis of cytologic examination of lymph nodes. When available, the following data were retrieved for each included dog at the time of diagnosis: signalment (breed, age, sex, and body weight), history (including previous administration of corticosteroids), tumor cytologic characterization according to the updated Kiel classification system, stage and substage according to the World Health Organization clinical staging system, PCV, serum total LDH activity, immunophenotype as determined by use of flow cytometry of a lymph node aspirate and peripheral blood as well as marrow blood, identification of bone marrow involvement, evidence of hypercalcemia, and type of treatment (first-line treatments and rescue protocols). Information pertaining to overall survival time, disease-free interval, occurrence of relapse, and cause of death was recorded. Whether a second malignancy developed during or after treatment was also recorded.

**Response assessment**—Response was classified as complete remission, partial remission, stable disease, or progressive disease. Complete remission indicated 100% reduction in size of all measurable lesions for at least 21 days, partial remission indicated > 50% but < 100% reduction of all measurable lesions for at least 21 days, stable disease indicated < 50% reduction or no change in size of all measurable lesions and lack of new neoplastic foci for at least 21 days, and progressive disease indicated an increase in > 25% of all measurable lesions or the appearance of new neoplastic foci.

**Statistical analysis**—Dogs that lived > 2 years after diagnosis were defined as long-term survivors. By the end of the study, dogs that had survived ≤ 2 years after diagnosis served as a comparison group. To reduce bias, only dogs that had died during the 2-year period were included in the comparison group.

The following potential predictor variables were investigated for an association with long-term survival by use of backward elimination logistic regression: age (≤ or ≥ 2 years), sex (male or female), breed (purebred or crossbred), body weight at diagnosis (≤ or ≥ 10 kg [22 lb]), PCV at diagnosis (≤ or ≥ 35%), serum LDH activity at diagnosis (high or within reference limits), ionized hypercalcemia at diagnosis (presence or absence), Kiel classification (centroblastic or other), immunophenotype (B-cell vs T-cell lymphoma), bone marrow involvement at diagnosis (presence or absence), lymphoma stage (V or I through IV) and substage (a or b) at diagnosis, corticosteroids administered within the 2 weeks prior to diagnosing lymphoma (yes or no), and number of relapses (none or ≥ 1). Age was categorized as or ≥ 2 years because lymphoma is generally considered more aggressive in young versus old dogs. Body weight was categorized as < or ≥ 10 kg because small breeds (ie, < 10 kg) are generally considered less susceptible to lymphoma; thus, if affected, the disease may have a different biological behavior. In addition, small breeds can have longer remissions than large breeds, attributable to higher dose intensity achieved with chemotherapy administered according to body surface. Packed cell volume was categorized as < or ≥ 35% because anemia is usually defined as PCV < 35%, and anemia may be associated with a decrease in survival time. Lymphoma stage was categorized as V or I through IV because stage V has been associated with poorer outcome, compared with the other stages. Univariate logistic regression was first used to identify variables with a value of P ≤ 0.25; these variables were then investigated further with multivariate logistic regression.
To verify whether a combination of outcome variables, rather than individual ones, may help in identifying dogs living > 2 years at diagnosis, collected data were further evaluated. The aforementioned dichotomous variables were assessed in dogs with lymphoma living > 2 years, and the most common combination of variables was identified; the proportion of dogs with that combination of those attributes was then calculated. The proportion of dogs with lymphoma living > 2 years with the same combination was also calculated. Sensitivity, specificity, positive and negative predictive values, and 95% CIs of the combination for predicting dogs living > 2 years were calculated.

The proportion of dogs surviving > 2 years that developed a second malignancy was compared with the proportion of dogs surviving ≤ 2 years by use of the Fisher exact test. A value of P < 0.05 was considered significant for all analyses. All analyses were performed with the aid of a computer software package.

**Results**

Dogs—One hundred twenty-seven dogs fulfilled the enrollment criteria. Among them, 13 (10%) survived > 2 years. Overall, survival rates at 3, 4, and 5 years were 4%, 3%, and 1%, respectively.

Dogs surviving > 2 years (long-term survivors) comprised 6 (46%) sexually intact males and 7 (54%) females (4 spayed and 3 sexually intact). Median age was 11 years (range, 5 to 14 years), and median body weight was 44.6 kg (98.1 lb; range, 5.0 to 62.0 kg [11 to 136.4 lb]). Six dogs were crossbred, 2 were Rottweilers, and there was 1 each of Pointer, Boxer, Yorkshire Terrier, Bernese Mountain Dog, and Doberman Pinscher. Median PCV at diagnosis of lymphoma was 43% (range, 35% to 49%). None of the dogs in this group had a PCV < 35%. Of 10 dogs in which serum LDH activity was determined at initial evaluation, 2 had activity within reference limits and 8 had high activity.

Three of the 13 long-term survivors had stage III, and 10 had stage IV lymphoma. Eleven had substages a, and 2 had substages b. Immunophenotype was B in all dogs. In 12 dogs, the morphological classification was centroblastic lymphoma, and in 1 dog, the classification was medium-cell macronucleated lymphoma. Two dogs were already receiving corticosteroids when first admitted to the hospital for initial staging. All dogs achieved a lasting complete remission after first-line chemotherapy with a CHOP-based regimen (n = 12) or doxorubicin alone (1). In 7 the 13 dogs, lymphoma recurred after a median of 177 days (range, 98 to 420 days). At relapse, dogs were treated again with a CHOP-based protocol (n = 4) or with a combined strategy (3), consisting of the same chemotherapeutic drugs administered according to the following scheme: l-asparaginase and vincristine (week 1), vincristine and cyclophosphamide (weeks 2 and 3), and doxorubicin (week 4).

Seven long-term survivors were alive and in complete remission from lymphoma at the end of the study, after a median follow-up period of 1,263 days (range, 740 to 1,783 days). One of them developed a prostatic carcinoma while still in complete remission from lymphoma. Six long-term survivors died during the study period, with a median survival time of 914 days (range, 740 to 2,058 days; Figure 1). Among these, 4 died because of another malignant tumor, including appendicular osteosarcoma (n = 3) and oral melanoma (1); in addition, 1 died from recurrent lymphoma and another died of a nonneoplastic disease.

Of the 114 dogs surviving ≤ 2 years, there were 61 (54%) females (of which 36 were spayed) and 53 (46%) males (of which 47 were sexually intact), with a median age of 8.5 years (range, 3 to 18 years) and median body weight of 50.7 kg (111.5 lb; range, 2.6 to 62.0 kg [5.7 to 136.4 lb]). The most represented breeds were German Shepherd Dog (n = 18), Boxer (7), Labrador Retriever (7), Rottweiler (5), and Dogo Argentino (4). The remaining were purebred but represented by 1 or 2 dogs/breed (n = 45) or were crossbred (28).

Information on PCV was available for 112 dogs, and the median PCV at initial evaluation was 39.5% (range, 16% to 63%). Eighty-four (75%) dogs had a PCV ≥ 35%, whereas the remaining 28 (25%) had a PCV < 35%. In 65 dogs, serum LDH activity was measured at diagnosis; in 19 (29%) of these dogs, it was within reference limits and in 46 (71%), it was high.

One of the 114 (1%) dogs living < 2 years had stage I lymphoma, 21 (18%) had stage III (15 with substages a and 6 with substages b), 58 (51%) had stage IV (36 with substages a and 22 with substages b), and 34 (30%) had stage V (14 with substages a and 20 with substages b). Of the 112 dogs in which immunophenotype was determined, 82 (73%) had B-cell lymphoma and 30 (27%) had T-cell lymphoma.

Of the 108 dogs in which the Kiel classification system was used to describe tumor morphology, 68 (63%) had centroblastic lymphoma, 11 (10%) had large-cell anaplastic lymphoma, 10 (9%) had medium-cell macronucleated lymphoma, 8 (7%) had immunoblastic lymphoma, 6 (6%) had lymphoblastic lymphoma, 3 (3%) had Burkitt’s-like lymphoma, 1 (1%) had plasmacytic lymphoma, and 1 (1%) had T-zone lymphoma.

At admission, 38 of the 114 (33%) dogs were already receiving corticosteroids. Regarding first-line chemotherapeutic regimens, 96 (84%) dogs were treated with a
CHOP-based protocol, 9 (8%) with doxorubicin alone, 5 (4%) with l-asparaginase (alone or combined with other drugs), 2 (2%) with lomustine alone, and 2 (2%) with chlorambucil alone.

Median survival time for dogs living < 2 years was 180 days (range, 4 to 724 days). At the end of the data collection period, 103 (90%) dogs were identified as having died as a result of disease, and 11 (10%) had died as a result of other causes. The dogs that died of other causes included 3 that developed a second malignancy (ie, gastric carcinoma, carcinoid, or melanoma). The proportion of dogs with a second malignancy was significantly (P < 0.001) higher in dogs that lived > 2 years (38%) than in dogs that lived ≤ 2 years (3%).

Factors associated with dogs with lymphoma living > 2 years—Results of backward elimination logistic regression analysis suggested that dogs that were crossbred and had no disease relapses were more likely to live for > 2 years than were other dogs. When multivariate analysis was used to assess independence of these variables, absence of relapse was significantly (P = 0.04) associated with dogs living > 2 years (OR, 3.45; 95% CI, 1.15 to 12.20) but not being crossbred (OR, 3.27; 95% CI, 0.95 to 11.42; P = 0.07).

Considering all variables at diagnosis, 11 of the 13 dogs with lymphoma that lived > 2 years after initial presentation had the following most common combination of characteristics: body weight ≥ 10 kg, PCV ≥ 35%, absence of ionized hypercalcemia, presence of centroblastic lymphoma, immunophenotype B, absence of bone marrow involvement, lymphoma stage I through IV, and no prior corticosteroid treatment. The same combination was present at diagnosis in 26 of 114 (23%) dogs surviving ≤ 2 years. The combination of characteristics had a sensitivity of 84.6% (95% CI, 53.7% to 97.3%), specificity of 77.2% (95% CI, 68.2% to 84.3%), and positive and negative predictive value of 29.7% (95% CI, 16.4% to 47.2%) and 97.8% (95% CI, 91.4% to 99.6%), respectively, to identify dogs with lymphoma living > 2 years.

Discussion

Over the past decade, great progress has been made in the treatment of high-grade multicentric lymphoma in dogs. Improved knowledge of biology of lymphoma, the optimal use of a variety of cytotoxic agents, and stratification of treatments on the basis of tumor and patient characteristics have gradually increased long-term survival. Despite these gains in cancer treatment, whether some dogs with lymphoma can be considered cured is not clear.

In 1986, Appelbaum et al published some preliminary data on peripheral blood stem cell transplantation, claiming that dogs receiving transplants were cured of their lymphoma. To the authors’ knowledge, this is the only report in veterinary medicine specifically addressing the issue of a cure in lymphoma patients. Nevertheless, according to their data, 3 of 12 dogs were alive and in complete remission at the end of the study; 334, 631, and 727 days following transplantation. Dogs in complete remission and alive after 1 to 2 years after diagnosis were assumed to be cured.

Five-year survival is often considered a landmark event for humans with cancer, representing a good indicator of therapeutic success. Because dogs have a shorter life cycle, it may be hypothesized that such a time frame could be reduced to 2 years in dogs. If this assumption is valid, then given the results of the present study involving prolonged follow-up in dogs with high-grade multicentric lymphoma, cure was not uncommon. An important fraction (10%) of dogs achieved long-term survival (> 2 years), lymphoma continued indefinitely to be in remission in most of them, and the cause of death was attributable to diseases other than lymphoma in 5 of the 6 long-term survivors that died before the study ended.

Multivariate logistic regression analysis indicated that only the absence of relapse was significantly associated with lymphoma in dogs living > 2 years. However, because of the low number of long-term survivors (ie, 13 dogs) and resulting limited statistical power, it cannot be excluded that additional variables might have been associated with long-term survival. By considering characteristics at diagnosis of dogs with lymphoma living > 2 years, it was possible to identify a common characteristics pattern among these dogs (85% of dogs affected). Data on these characteristics were retrieved from the clinical history, physical examination findings, and laboratory analysis results without the need for more sophisticated tests and included the following: body weight, PCV, calcemia, morphological description of lymphoid cells, immunophenotype, bone marrow status, clinical stage, and use of corticosteroids prior to diagnosis. Accordingly, 11 of the 13 dogs living > 2 years concurrently had at diagnosis a body weight ≥ 10 kg, PCV ≥ 35%, absence of ionized hypercalcemia, centroblastic lymphoma, immunophenotype B, absence of bone marrow involvement, lymphoma stage I through IV, and lack of pretreatment with corticosteroids. The same combination was evident in a considerably smaller percentage (23%) of dogs living ≤ 2 years.

This combination of results yielded a sensitivity of 85% and a specificity of 77% to identify dogs with lymphoma living beyond 2 years. Although the specificity of this combination for detection of long-term survivors was not high, it is worth noticing that the negative predictive value was very high (98%) given the prevalence of long-term survivors in our study sample, suggesting that when the aforementioned factor combination was not present, dogs with lymphoma were very unlikely to survive > 2 years. The predictive values obtained, however, are specific to the conditions in the present study and in other settings would vary according to the prevalence of long-term survivors in those settings. The presence of each of the combination variables by itself has been shown by others to be significantly related to survival time. Consequently, it was not surprising that the combination of these was coupled with longer survival. Because these variables were not influenced by the adopted chemotherapeutic protocol in our analyses, their combination may be useful in clinical practice to estimate survival expectation. However, additional validation is required to confirm the combination’s value in predicting the probability of long-term survival in dogs with lymphoma.
Unexpectedly, median body weight was quite large in both groups (44.6 kg in dogs surviving > 2 years and 50.7 kg in dogs surviving ≤ 2 years). Any breed of dog is susceptible to developing lymphoma; therefore, we would have expected these body weight values to be in the range of 20 to 25 kg. The fact that body weight varied widely in both dog groups suggests that each group was heterogeneous; however, because median body weights and ranges were similar between survivor groups, the bias associated with the unexpectedly high values was likely minor.

Although long-term survival was achieved in approximately 10% of dogs with high-grade multicentric lymphoma, possible treatment-related long-term effects were evident. Indeed, second malignancies developed in 5 of the long-term survivors and accounted for most (67%) deaths, with recurrent disease and other causes accounting for 17% of deaths each. By contrast, in dogs surviving < 2 years, the main cause of death remained progressive lymphoma (n = 103 [90%]). The risk of dying from a second malignancy ranked third among the long-term survivors, with only 3 dogs developing another malignancy. However, it is possible that the dogs in this group died before living long enough to develop a second type of cancer.

The extent to which development of a genetic predisposition for developing cancer or the potential of a specific type of cancer to predispose affected dogs to second malignancies is unclear. Importantly, in human oncology, evidence has accumulated indicating that a considerable amount of second malignancies are attributable to chemotherapy, mainly to alkylating agents.\(^5\)\(^6\) Multidrug chemotherapy, which represents a milestone for the treatment of high-grade multicentric lymphoma in dogs, involves a combination of antineoplastic drugs, each with antilymphoma properties and nonoverlapping mechanisms of action. Most chemotherapeutic agents possess carcinogenic properties, thereby raising concern about possible risks in relation to development of a second cancer. In human oncology, patients with non-Hodgkin’s lymphoma receiving CHOP-like chemotherapy are at increased risk for a second cancer relative to other such patients, including other hematologic malignancies and solid tumors (eg, colorectal carcinoma or lung, brain, kidney, and prostate cancer).\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\) Second bone malignancies are more common after childhood cancer\(^11\)\(^12\); nevertheless, the same association was not observed in the present study, as the 3 dogs that developed osteosarcoma were already adults (7, 8, and 10 years of age) when lymphoma was first diagnosed. Another dog developed oral melanoma, whereas an additional dog developed prostatic carcinoma.

More accurate diagnostic testing and better therapeutic approaches for dogs with high-grade multicentric lymphoma have lead to improved outcomes in affected dogs. Lack of the combination of variables at diagnosis that we identified may help to identify dogs with lymphoma that will not live longer than 2 years. Conversely, early detection of long-term survivors remains difficult. Absence of relapse, which was associated with dogs living > 2 years, is a follow-up variable and as such cannot be useful at first diagnosis. Furthermore, long-term survival of dogs with high-grade multicentric lymphoma may be linked to an increased chance of developing a second malignancy, particularly osteosarcoma. Owners of long-term surviving dogs need to be informed about potential late development of new cancers, and well-timed follow-up appointments are required for their early detection. Achievement of a balance between treatment effectiveness and minimization of hazards late in the course of treatment may represent a challenge for veterinary oncologists.

References


From this month’s AJVR

Pharmacokinetics and antinociceptive effects of oral tramadol hydrochloride administration in Greyhounds

Butch KuKanich and Mark G. Papich

Objective—To determine the pharmacokinetics of tramadol, the active metabolite O-desmethyltramadol, and the metabolites N-desmethyltramadol and N,O-didesmethyltramadol after oral tramadol administration and to determine the antinociceptive effects of the drug in Greyhounds.

Animals—6 healthy 2- to 3-year-old Greyhounds (3 male and 3 female), weighing 25.5 to 41.1 kg.

Procedures—A mean dose of 9.9 mg of tramadol HCl/kg was administered PO as whole tablets. Blood samples were obtained prior to and at various points after administration to measure plasma concentrations of tramadol and its metabolites via liquid chromatography with mass spectrometry. Antinociceptive effects were determined by measurement of pain-pressure thresholds with a von Frey device.

Results—Tramadol was well tolerated, and a significant increase in pain-pressure thresholds was evident 5 and 6 hours after administration. The mean maximum plasma concentrations of tramadol, O-desmethyltramadol, N-desmethytramadol and N,O-didesmethyltramadol were 215.7, 5.7, 379.1, and 237.2 ng/mL, respectively. The mean area-under-the-curve values for the compounds were 592, 16, 1,536, and 1,013 h•ng/mL, respectively. The terminal half-lives of the compounds were 1.1, 1.4, 2.3, and 3.6 hours, respectively. Tramadol was detected in urine 5 days, but not 7 days, after administration.

Conclusions and Clinical Relevance—Oral tramadol administration yielded antinociceptive effects in Greyhounds, but plasma concentrations of tramadol and O-desmethyltramadol were lower than expected. Compared with the approved dose (100 mg, PO) in humans, a mean dose of 9.9 mg/kg, PO resulted in similar tramadol but lower O-desmethyltramadol plasma concentrations in Greyhounds. (Am J Vet Res 2011;72:256–262)