Response rate after administration of a single dose of doxorubicin in dogs with B-cell or T-cell lymphoma: 41 cases (2006–2008)

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Objective—To determine the response rate after administration of a single dose of doxorubicin in dogs with B-cell or T-cell multicentric or thymic lymphoma.

Design—Retrospective case series.

Animals—41 client-owned dogs with lymphoma.

Procedures—Medical records of dogs in which lymphoma was diagnosed between February 2006 and October 2008 were reviewed. Entry criteria included that dogs had a confirmed lymphoma that was immunophenotyped to be of B-cell or T-cell origin. Only dogs that received doxorubicin alone as their first chemotherapy treatment and were evaluated 1 week later were included in the study. Dogs were excluded when they had received prior treatment with corticosteroids. Medical records were reviewed to obtain signalment, stage and substage of lymphoma, and immunophenotype and to determine whether the dog had hypercalcemia at the time of diagnosis.

Results—Dogs with T-cell lymphoma had a significantly lower response rate to doxorubicin than did dogs with B-cell lymphoma. Twenty-five of 29 (86.2%) dogs with B-cell lymphoma had a complete response, compared with 2 of 12 dogs in the T-cell group that had a complete response. The overall response rate of dogs with B-cell lymphoma was 100%, compared with a response rate of 50% in dogs with T-cell lymphoma.

Conclusions and Clinical Relevance—Standard-of-care chemotherapy protocols for the treatment of dogs with lymphoma include doxorubicin. Many dogs with T-cell lymphoma did not respond to doxorubicin; therefore, multiagent protocols containing doxorubicin may not be optimal. Alternative protocols should be considered for dogs with T-cell lymphoma that do not respond to doxorubicin. (*J Am Vet Med Assoc* 2010;237:1052–1055)

Lymphoma has been reported to account for between 7% and 24% of all malignancies in dogs.[1–3] The annual incidence rate has been estimated to be between 13 and 34 cases/100,000 at-risk dogs.[2–7] With few exceptions, lymphoma is characterized as a multifocal disease, and chemotherapy is the mainstay of treatment. Combination chemotherapy protocols are generally considered superior to single-agent protocols and are most commonly recommended for the treatment of dogs with lymphoma.[2,6,8] Early protocols were based on a combination of vincristine, cyclophosphamide, and prednisone. Studies[6,7,9,10] revealed that the addition of doxorubicin to these protocols significantly increased the first-remission duration and survival time in dogs with lymphoma.

Doxorubicin is used in the treatment of a wide variety of malignancies, and it is considered the single most effective drug against lymphoma in dogs.[10–12] It is an anthracycline antimicrobial that has multiple mechanisms of action, including intercalation of DNA, formation of free radicals, and inhibition of topoisomerase enzymes.

Abbreviation

CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone

Response rate for administration of doxorubicin alone in dogs with lymphoma is reported to be between 59% and 81%.[4,8,13,14] Although many variations exist, current standard-of-care chemotherapy protocols for the treatment of dogs with lymphoma are CHOP-based protocols that include doxorubicin in combination with vincristine, cyclophosphamide, L-asparaginase, and prednisone.

Two of the most commonly reported prognostic factors in dogs with lymphoma are substage and immunophenotype. Dogs classified as substage b (clinical signs evident at the time of diagnosis) have a shorter survival time than do dogs that are substage a (no signs of illness at the time of diagnosis).[7,15,16] The T-cell lymphomas account for between 20% and 30% of all lymphomas in dogs, and intermediate- to high-grade T-cell lymphomas are associated with significantly shorter remission and survival times, compared with outcomes for B-cell lymphomas.[1–3,5,14,17,18] The objective of the study reported here was to evaluate the response of dogs with T-cell or B-cell lymphoma to a single dose of doxorubicin. Our hypothesis was that dogs with T-cell lymphoma would have a lower response rate to doxorubicin than would dogs with B-cell lymphoma; therefore, treatment in accordance with standard CHOP-

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based combination chemotherapy protocols may not be optimal for dogs with T-cell lymphoma.

Materials and Methods

Case selection—Medical records of dogs with lymphoma examined at Southwest Veterinary Oncology between February 2006 and October 2008 were examined. Dogs were included in the study when they had newly diagnosed lymphoma that had been immunophenotyped as either B-cell or T-cell origin. Only dogs that received doxorubicin alone as their first chemotherapy treatment and were evaluated 1 week later were included in the study. Dogs were excluded from the study when they received treatment with corticosteroids prior to the administration of doxorubicin.

Medical records review—Medical records from each dog were reviewed to obtain the signalment (age, sex, and breed), stage and substage of lymphoma, and results of immunophenotyping and to determine whether they had hypercalcemia at the time of admission. Lymphoma was diagnosed on the basis of cytologic or histologic examination of a sample obtained from a peripheral lymph node. Immunophenotyping was performed in accordance with standard procedures on lymph node aspirates submitted to either of 2 veterinary diagnostic laboratories.[a,b]

Pending results of immunophenotyping, each dog received 1 dose of doxorubicin administered IV at a dose of 30 mg/m^2 for dogs weighing ≥ 10 kg (22 lb) or 1 mg/kg (0.45 mg/lb) for dogs weighing < 10 kg. Additional treatment (via a single-agent doxorubicin protocol or a multidrug protocol) was determined on the basis of treatment response and after consultation with the owner.

All dogs were evaluated 7 days after administration of the dose of doxorubicin to assess the response to treatment. All evaluations were performed by a single board-certified veterinary oncologist (MKK). Response was characterized on the basis of the resolution or decrease in size of peripheral lymphadenopathy or mediastinal mass (or both) as well as an improvement in hypercalcemia for those dogs in which it had been detected. Dogs were assigned to 1 of 3 response categories on the basis of physical examination findings, results of hematologic analysis, and results of any other follow-up diagnostic tests that were performed 1 week after initial treatment. Complete response was defined as complete resolution of any physical examination, clinicopathologic, or imaging abnormalities associated with the lymphoma. Dogs were considered to have had a partial response when there was at least a 50% decrease in the size of measurable lymph nodes or mediastinal masses and any previous elevation in serum calcium concentration, without the appearance of any new lesions. Dogs with a decrease of < 50% were considered to have had no response to the doxorubicin.

Statistical analysis—A Student *t* test was used to compare the 2 groups with regard to age and body weight. All other statistical analyses were performed by use of χ^2 tests with a Williams correction. Results were considered significant at values of $P < 0.05$.

Results

Medical records of 180 dogs with newly diagnosed lymphoma between February 2006 and October 2008 were reviewed. Of these, 41 met the inclusion criteria for the study.

Age of the 41 dogs ranged from 3 to 13 years (mean, 8 years; median, 7.8 years). Twenty-two dogs were neutered males, 17 were spayed females, and 2 were sexually intact males. Body weight of all dogs in the study ranged from 9.5 to 72 kg (20.9 to 158.4 lb), with a mean of 29.9 kg (65.8 lb) and a median of 28 kg (61.6 lb). Thirty breeds of dogs were represented, with the most common being Rottweilers (n = 3 dogs), Golden Retrievers (3), and Boxers (3).

Twenty-nine of 41 (70.7%) dogs had B-cell lymphoma, and the other 12 (29.3%) dogs had T-cell lymphoma. Age of the dogs with B-cell lymphoma ranged from 4 to 13 years (mean, 8.4 years; median, 8.3 years), whereas age of the dogs with T-cell lymphoma ranged from 3 to 10 years (mean, 7.4 years; median, 7.4 years). Body weight of the dogs with B-cell lymphoma ranged from 9.5 to 55.7 kg (20.9 to 122.5 lb), with a mean of 27.8 kg (61.2 lb) and a median of 27.6 kg (60.7 lb). Body weight of the dogs with T-cell lymphoma ranged from 11.8 to 72 kg (26 to 158.4 lb), with a mean of 34.9 kg (76.8 lb) and a median of 33.7 kg (74.1 lb). Of the 29 dogs with B-cell lymphoma, 15 were neutered males, 2 were sexually intact males, and 12 were spayed females. Of the 12 dogs with T-cell lymphoma, 7 were neutered males and 5 were spayed females. There were no significant differences between the 2 groups with respect to age, body weight, or sex.

In 4 dogs, lymphoma was diagnosed on the basis of histologic findings for a specimen obtained from an enlarged peripheral lymph node. In the remaining 37 dogs, lymphoma was diagnosed on the basis of cytologic findings from a specimen obtained from an enlarged peripheral lymph node. In all dogs, results were consistent with an intermediate- to high-grade lymphoma.

Dogs were staged in accordance with the World Health Organization clinical staging system for lymphoma in domestic animals.[3] Of the 29 dogs with B-cell lymphoma, 15 (51.7%; which included 1 dog with a mediastinal mass) were classified as stage 3, 9 (31.0%) were classified as stage 4, and 5 (17.2%; which comprised 3 with ocular involvement and 2 with bone marrow involvement) were classified as stage 5. Twenty-six of 29 (89.7%) dogs with B-cell lymphoma were classified as substage a, and 3 (10.3%) were classified as substage b. Of the 12 dogs with T-cell lymphoma, 10 (83.3%; which included 1 dog with a mediastinal mass) were classified as stage 3, 1 (8.3%) was classified as stage 5 on the basis of ocular involvement, and 1 (8.3%) had thymic lymphoma. Nine of 12 dogs with T-cell lymphoma were classified as substage a, and 3 were classified as substage b. No significant differences were detected between the 2 groups with respect to stage or substage (**Table 1**).

Three dogs, all of which had T-cell lymphoma, had an elevated serum calcium concentration at admission. Only one of these dogs had a mediastinal mass. The proportion of dogs with hypercalcemia differed significantly ($P = 0.007$) between the 2 groups (Table 1).

The overall response rate (complete plus partial responses) of dogs with B-cell lymphoma to administration of a single dose of doxorubicin was 100%. Twenty-five of 29 (86.2%) dogs with B-cell lymphoma had a complete response to the doxorubicin, and 4 (13.8%) dogs had a par-

Table 1—Disease characteristics of dogs with B-cell (n = 29) or T-cell (12) lymphoma.

Variable	B-cell No. (%)	T-cell No. (%)	*P* value*
Stage III	15 (51.8)	10 (83.4)	0.235
Stage IV	9 (31.0)	0 (0)	0.055
Stage V	5 (17.2)	1 (8.3)	0.476
Thymic lymphoma	0 (0)	1 (8.3)	0.156
Substage a	26 (89.7)	9 (75)	0.652
Substage b	3 (10.3)	3 (25)	0.270
Hypercalcemia	0 (0)	3 (25)	0.007

*Values were considered significantly different at $P < 0.05$.

tial response. The overall response rate of dogs with T-cell lymphoma to administration of a single dose of doxorubicin was 50% (2/12 dogs had a complete response, and 4 dogs had a partial response; 6 dogs had no response). Dogs with B-cell lymphoma differed significantly from dogs with T-cell lymphoma with regard to overall response rate ($P < 0.001$), complete response rate ($P = 0.013$), and the proportion of dogs with no response to a single administration of doxorubicin ($P < 0.001$), but the 2 groups did not differ significantly ($P = 0.197$) with regard to partial response rate.

Discussion

Overall, the demographics for the dogs in the study reported here were consistent with those reported in other studies[11,16,19,20] of dogs with lymphoma. Analysis of results of the present study indicated that dogs with T-cell lymphoma have a significantly lower response rate to doxorubicin than do dogs with B-cell lymphoma. The overall response rate to doxorubicin in this study was 85.4% (35/41 dogs), which is consistent with the value reported in other studies.[4,8,13,14] However, when the response rate was evaluated on the basis of immunophenotype, a significantly ($P < 0.001$) higher proportion (100%) of dogs with B-cell lymphoma had a response to the doxorubicin, compared with only 50% of the dogs with T-cell lymphoma. Additionally, of the 6 dogs with T-cell lymphoma that responded, only 2 (which represented only 2/12 dogs in that group) had a complete response to the doxorubicin. Although the number of dogs was small, no differences were detected between the dogs with T-cell lymphoma that did or did not respond to the doxorubicin. Few studies have been conducted to evaluate the effect of immunophenotype on response to treatment. In 2 studies,[1,5] a significant relationship was not detected. To the authors' knowledge, no studies have been conducted to specifically evaluate the manner in which immunophenotype affects the response to doxorubicin, although investigators in 1 study[21] found that dogs with T-cell lymphoma had a decreased chance of remission when treated in accordance with a multiagent CHOP-based protocol. Immunophenotype is recognized as one of the most important prognostic factors in dogs with lymphoma; dogs with intermediate- to high-grade T-cell lymphoma have shorter remission and survival times.[1,5,14,18] Although doxorubicin-based chemotherapy protocols are generally considered optimal for the treatment of lymphoma in dogs, this may not be true for those dogs with T-cell lymphoma that do not respond to doxorubicin. Lack of response to doxorubicin would substantially decrease the overall efficacy of these protocols with regard to their ability to induce or maintain remission in these dogs; thus, it may contribute to a more guarded prognosis. This is supported by a recent report[22] in which investigators detected an improvement in both remission duration and overall survival time in dogs with T-cell lymphoma that were treated in accordance with a non–CHOP-based multiagent chemotherapy protocol.

One limitation of the study reported here was the small sample size. Although the number of dogs was low, there was a significant difference in response rate between the 2 groups, which we believe would be true with a larger sample size. Lack of complete staging in all dogs is another limitation of this study. All dogs in the study, except for 1, had multicentric lymphoma; however, complete staging, including thoracic radiography, abdominal ultrasonography, and evaluation of a bone marrow aspirate, was not performed in all dogs. This is a limitation of many studies of dogs with lymphoma. Dogs were classified as having stage 4 lymphoma when they had palpable enlargement of the liver or spleen and stage 5 lymphoma when they had evidence of ocular or bone marrow involvement on the basis of concurrent anterior uveitis or circulating lymphoblasts detected during evaluation of blood samples, respectively. Had all dogs been fully staged, it is possible that there may have been more dogs with stage 4 or 5 disease in both groups. Although stage of disease has been found to be of prognostic importance in some studies,[5,8,23] its influence on prognosis is inconsistent and the role of stage of disease in predicting prognosis remains unclear.

The study reported here revealed that dogs with T-cell lymphoma had a relatively low response rate to administration of a single dose of doxorubicin. Only 2 of 12 dogs with T-cell lymphoma in this study had a complete response to doxorubicin. Dogs that achieve a complete remission have a better long-term prognosis.[17–19] Standard-of-care chemotherapy protocols for dogs with lymphoma include doxorubicin, and for those dogs with T-cell lymphoma that do not respond to doxorubicin, use of these protocols may not offer the best chance of long-term survival because these dogs receive attenuated treatment with cyclophosphamide, vincristine, prednisone, and L-asparaginase. Dogs with T-cell lymphoma may benefit from receiving doxorubicin first to enable clinicians to assess treatment response and increase the doses or administration frequency of the remaining drugs or to institute alternative protocols for dogs that do not respond. Larger studies from a wider geographic area will be required to further evaluate the possibility of improving the prognosis for dogs with T-cell lymphoma through alteration of the chemotherapy protocols.

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From this month's *AJVR*

Evaluation of 12- and 24-month survival rates after treatment with masitinib in dogs with nonresectable mast cell tumors

Kevin A. Hahn et al

Objective—To evaluate the effectiveness of masitinib for the treatment of nonresectable mast cell tumors (MCTs) in dogs at 12 and 24 months after onset of treatment.

Animals—132 dogs with nonresectable grade 2 or 3 MCTs.

Procedures—Dogs received masitinib (12.5 mg/kg/d, PO; n = 106) or a placebo (26). After 6 months, treatment was extended with tumor assessments at 3-month intervals until detection of disease progression. Endpoints were tumor response and overall survival rate and time.

Results—In dogs with nonresectable MCTs, masitinib significantly improved survival rate, compared with results for the placebo, with 59 of 95 (62.1%) and 9 of 25 (36.0%) dogs alive at 12 months and 33 of 83 (39.8%) and 3 of 20 (15.0%) dogs alive at 24 months, respectively. Median overall survival time was 617 and 322 days, respectively. Tumor control at 6 months had a high predictive value for 24-month survival, with high specificity (88%) and sensitivity (76%), whereas short-term tumor response (within 6 weeks) had a poor predictive value. Complete responses at 24 months were observed in 6 of 67 (9.0%) dogs with nonresectable MCTs treated with masitinib.

Conclusions and Clinical Relevance—Masitinib significantly increased survival rates at 12 and 24 months in dogs with nonresectable MCTs. Control of disease at 6 months, but not best response at 6 weeks, was predictive of long-term survival in dogs treated with masitinib, which suggested that short-term response may be irrelevant for assessing clinical efficacy of tyrosine kinase inhibitors for treatment of MCTs. (*Am J Vet Res* 2010;71:1354–1361)