Usefulness of chemotherapy for the treatment of very elderly dogs with multicentric lymphoma

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OBJECTIVE
To evaluate factors for associations with duration of first remission and survival time in dogs ≥ 14 years of age with stage III to V multicentric lymphoma.

DESIGN
Retrospective cohort study.

ANIMALS
29 dogs ≥ 14 years of age with multicentric lymphoma treated with a chemotherapy protocol at dosages used for younger dogs (n = 22) or with prednisolone alone (7).

PROCEDURES
Various data were collected from the medical records, including treatment response and related adverse events. Survival analysis was performed to determine duration of first remission and survival time (from start of chemotherapy), and these outcomes were compared between various groupings.

RESULTS
The 7 (24%) dogs that received prednisolone alone had a median survival time of 27 days and were excluded from further analysis. Complete clinical remission was achieved in 21 of the 22 (95%) remaining dogs; 1 (5%) achieved partial remission. Median duration of first remission was 181 days. Anemic dogs had a briefer remission period (median, 110 days) than nonanemic dogs (median, 228 days). Median survival time for all 22 dogs was 202 days, with estimated 1- and 2-year survival rates of 31% and 5%, respectively. Six (27%) dogs had adverse events of chemotherapy classified as grade 3 or worse.

CONCLUSIONS AND CLINICAL RELEVANCE
Survival time was substantially longer in dogs treated with a chemotherapy protocol versus prednisolone alone. Findings suggested that the evaluated chemotherapy protocols for lymphoma were beneficial for and tolerated by very elderly dogs, just as by younger dogs, and need not be withheld, or dosages adjusted, because of age alone. (J Am Vet Med Assoc 2018;252:852–859)

With improvements in healthcare, pet dogs can be expected to live longer and veterinarians can be expected to evaluate and treat more elderly dogs than in the past. The role of chemotherapy in extending survival time and maximizing quality of life for most dogs with lymphoma has been well established; however, when dealing with lymphoma in older dogs, veterinarians and pet owners may be unsure whether provision of chemotherapy would be justified. This uncertainty may arise from concerns about advanced age increasing the risk of adverse effects of chemotherapy, the ability of older dogs to tolerate the same adverse effects as younger dogs, or the impact of comorbidities on the disease, treatment, and overall prognosis as well as from a lack of published evidence regarding the chemoresponsiveness of lymphoma in older dogs.

Although dogs ≥ 14 years of age are reportedly more likely to have B-cell lymphoma than T-cell lymphoma,¹ the effect (if any) of age on prognosis for dogs with nonindolent lymphoma that received chemotherapy has not been clearly established. Most studies have shown no effect of age on prognosis. For example, investigators in one study² found that older dogs had longer remission periods and survival times than younger dogs with the same disease, whereas investigators in another study³ demonstrated that the remission period and survival time for dogs with lymphoma decreased with increasing age. Investigators in the second study³ suggested that older dogs that achieved clinical remission were more likely to have their treatment ceased or...
be euthanized while in remission than younger dogs and believed that this reflected owners’ reluctance to pursue treatment for older dogs. Our impression is that owners of elderly dogs with lymphoma perceive their canine companions as frailer, the risks for toxic effects of chemotherapy greater, and chances for long survival times lower than might be expected for younger dogs. Similarly, older people with lymphoma are reportedly much less likely to receive treatment than younger people, and the decision of whether to treat appears to be based on age alone rather than the presence of comorbidities.4

The median age of human patients with DLBCL is 70 to 75 years, and the disease is more common in males than females.4 Factors indicative of a poorer prognosis in humans with DLBCL include age > 60 years, worsening Eastern Cooperative Oncology Group performance status, more advanced disease stage, extranodal disease at > 1 site, and high serum lactate dehydrogenase activity. Of these variables, age at diagnosis is a major prognostic factor, and the lymphoma-specific death rate for DLBCL patients > 75 years of age is 40 times that for similar patients < 45 years of age.4

A case series5 regarding 140 people > 70 years of age with DLBCL revealed that cardiovascular complications, peripheral neuropathy, and diabetic complications caused by prednisone were the most common comorbidities. Even still, DLBCL and not comorbid disease was the noted cause of death for 76% of these patients. In another study6 of human DLBCL patients > 80 years of age, 87% of whom had at least 1 comorbidity, death was attributed to lymphoma for 58% of patients and to comorbidities for only 14%.

In contrast, survival times are briefer for older (vs younger) people with lymphoma, who already have reduced ability to perform activities of daily living prior to starting chemotherapy.7 Dementia, osteoporosis, depression, falls, and incontinence are stronger predictors of poor outcome than all other lymphoma-specific prognostic factors and age alone,7 suggesting that frailty is a stronger negative predictor of outcome than is the lymphoma itself, and a robust elderly person with lymphoma can still have a good outcome with treatment.

Additional challenges in the treatment of elderly human lymphoma patients include the potential for drug interactions with various other existing medications and concern about the potential for toxic effects of chemotherapy; and both challenges often lead to selection of lower dosage treatment. Lower-intensity chemotherapy protocols have been evaluated in very elderly (> 80 years) people with DLBCL, and although these protocols are associated with fewer toxic effects than higher dosage protocols, survival times are also lower, particularly when anthracyclines are withheld.8 The exception has been chemotherapy protocols that include rituximab, which reportedly provide acceptable survival times, with lower rates of hospitalization or death due to toxic effects of treatment.9,10

The age at which dogs could be considered very elderly has not been established. Although the definition of geriatric dogs commonly used in some veterinary publications11-13 is > 8 years of age, this definition does not precisely capture the more extreme age group used for humans. A British study14 involving > 3,000 dogs revealed that 26% lived to 14 years and 8% lived to 15 years. Estimates indicate that the human age equivalent would be 66 to 75 years for a 14-year-old dog weighing < 10 kg (22 lb), 75 to 90 years for a dog of similar age weighing 10 to 23 kg (22 to 51 lb), 82 to 89 years for a dog of similar age weighing 23 to 39 kg (51 to 66 lb), and 89 to 95 years for a dog of similar age weighing > 39 kg (66 lb).15 Consequently, we propose that age ≥ 14 years can be used to represent very elderly dogs, a population that could be expected to be distinct from the general population of dogs considered geriatric.

To the authors’ knowledge, no descriptive studies have been reported regarding very elderly dogs with lymphoma, and prognostic factors for this group specifically are unknown. The purpose of the study reported here was to retrospectively characterize duration of first remission, survival time, and adverse effects of chemotherapy for dogs ≥ 14 years of age with multicentric lymphoma and evaluate putative prognostic factors for associations with both outcomes.

Materials and Methods

Animals

Medical records of a private veterinary oncology service were searched to identify dogs ≥ 14 years of age in which multicentric lymphoma was diagnosed from 2007 to 2015. For this study, the diagnosis of multicentric lymphoma was required to have been made on the basis of cytologic analysis of lymph node aspirate samples (intermediate- to large-cell lymphoma) or histologic examination of lymph node biopsy specimens (intermediate- to high-grade lymphoma). Immunophenotype was determined through immunohistochemical or immunocytochemical analysis.

Medical records review

Medical records were reviewed and pretreatment data collected when available regarding signalment, histologic grade of tumor, results of CBC and serum biochemical analysis, recorded findings of thoracic radiography and abdominal ultrasonography, and any comorbidities. Lymphoma had been clinically staged in all dogs at diagnosis in accordance with World Health Organization guidelines.16 Hematologic (neutropenic) and gastrointestinal adverse events were retrospectively graded in accordance with the VCOG-CTCAE.17 Dose reductions and treatment delays as well as reasons for them (whether neutropenia, gastrointestinal signs, or other) were recorded.

Chemotherapy protocol

Dogs considered to have received chemotherapy were treated with a COP (Appendix 1) or L-CHOP (Appendix 2) protocol. Mitoxantrone was substituted for doxorubicin for dogs with cardiac abnormali-
ties. Drug dosages were not reduced for patients on the basis of their age. Additional treatment was offered at relapse.

Response assessment

Three or more target lymph nodes were identified at the start of chemotherapy and measured with calipers. Assessment of remission was based on VCOG-CTCAEs (categories of none, 1 to 2, or > 2) between the 2 chemotherapy protocols. The Kaplan-Meier product-limit method and Cox proportional hazards analysis were used to evaluate associations between putative prognostic factors and outcome (duration of first remission and survival time).

All dogs that started chemotherapy with a COP or L-CHOP protocol were included in the analysis of treatment response and survival time. Duration of first remission was defined as the period from the start of chemotherapy until first evidence of progressive disease. Dogs with disease still in remission at the last point of contact were censored from survival analysis at that point. Survival time was defined as the period from the start of chemotherapy until death and for some dogs included a second remission. Patients lost to follow-up were censored from survival analysis at the last day of contact.

In both survival analyses, body weight was evaluated as a continuous predictor variable. Categorical predictor variables included clinical stage and substage of lymphoma, body weight category (greater vs less than median weight), presence of anemia (PCV < 35%) at diagnosis (yes vs no), and chemotherapy protocol (COP vs L-CHOP). Factors with a P value < 0.10 on univariate analysis were evaluated in a multivariate Cox model through a forward selection process. Values of P < 0.05 were considered significant.

Results

Dogs

Twenty-nine dogs, ranging in age from 14 to 17 years, were considered for inclusion in the study. Seven (24%) of these dogs (four 14-year-olds, two 15-year-olds, and one 16-year-old) were not treated with the COP or L-CHOP protocol, receiving only prednisolone. Median survival time for the 7 dogs was 27 days (range, 13 to 59 days). These dogs were excluded from further analyses.

The remaining 22 dogs were included in the study. This group included 10 (45%) mixed-breed dogs, 2 (9%) Jack Russell Terriers, 2 (9%) Golden Retrievers, and 1 (5%) dog each of various other breeds. All dogs were neutered; 13 (59%) were male, and 9 (41%) were female. Median body weight was 13 kg (29 lb; range, 4 to 40 kg [9 to 88 lb]).

Diagnosis

For 14 (64%) dogs, multicentric lymphoma had been diagnosed by histologic examination of lymph node biopsy specimens; all 14 had high-grade lymphoma. For 10 (45%) dogs (including 2 with histologic assessment), multicentric lymphoma had been diagnosed by cytologic analysis of lymph node aspirate samples. Aspirate samples from 8 dogs with a cytologic diagnosis but no histologic assessment contained 80% to 90% intermediate- to large-sized cells, and samples from 6 dogs contained mitotic figures; these findings were considered consistent with non-indolent lymphoma.

Results of immunophenotyping were available for 20 (91%) dogs. Nineteen (95%) of these dogs had B-cell lymphoma, and 1 (5%) dog had T-cell lymphoma. No bone marrow aspirate samples were collected from any dog.

Comorbidities

Results of pretreatment cardiac auscultation were available for 20 (91%) dogs. Four (20%) dogs had abnormalities, including subclinical cardiac murmur (n = 2 [10%]), cardiac murmur plus clinical signs that improved with pimobendan administration (1 [5%]), and enlarged cardiac silhouette on radiography and decreased fractional shortening on echocardiography (1 [5%]).

Results of pretreatment serum biochemical analysis and urinalysis were available for 21 (95%) dogs. Five (24%) of these dogs were azotemic with a urine specific gravity < 1.020, and 1 (5%) dog (with B-cell lymphoma) was mildly hypercalcemic (serum calcium concentration, 3.04 mmol/L [reference range, 1.98 to 3.00 mmol/L]; ionized calcium concentration not measured). Results of pretreatment hematologic testing were available for 21 (95%) dogs. Six (29%) dogs were anemic (median PCV, 31.5%; range, 27% to 33%).

Other preexisting comorbidities included history of pancreatitis with or without high serum canine pancreas-specific lipase activity (n = 3 [14%]), hyperadrenocorticism (2 [9%]), urinary incontinence (1 [5%]), and lower motor neuron paresis (1 [5%]).

Clinical staging

Thoracic radiography had been performed for 17 (77%) dogs; none had a visible cranial mediastinal mass or other intrathoracic abnormality (other than typical aging-related changes). Eleven (50%) dogs had abdominal ultrasonography performed, of which 9 had hepatic enlargement, splenic enlargement, or both; these abnormalities were presumed to be attributable to lymphoma.

Because staging had not been completed for all dogs, disease stage was instead classified by minimum clinical stage. Seven (32%) dogs were classified...
as having minimum stage III disease, 12 (55%) as having minimum stage IV disease, and 3 (13%) as having stage V disease. All dogs with clinical stage V disease had circulating lymphoblasts identified in a peripheral blood smear. Eighteen (82%) dogs had substage A disease, and 4 (18%) had substage B disease. Clinical signs of dogs with substage B disease included inappetence, cough, diarrhea, lethargy, weakness, and pyrexia.

**Treatment and response**

Four (18%) dogs were treated with the COP protocol, and 18 (82%) were treated with the L-CHOP protocol. All 4 dogs with abnormal findings of cardiac auscultation were treated with the L-CHOP protocol but received mitoxantrone instead of doxorubicin. One dog with concurrent T-cell chronic lymphoid leukemia received chlorambucil and lomustine after completing the L-CHOP protocol.

Twenty-one (95%) dogs achieved complete remission, and 1 (5%) dog achieved partial remission. This latter dog was the only dog with confirmed T-cell lymphoma.

On relapse, 6 dogs received further treatment; all had been initially treated with the L-CHOP protocol. One dog received only prednisolone, with no response. Three dogs received additional L-CHOP treatment, to which 1 dog had no response, 1 achieved partial remission, and 1 achieved complete remission. Two dogs received other chemotherapeutic agents (1 or more of lomustine, actinomycin-D, procarbazine, melphalan, cytosine arabinoside, and bleomycin), with no response.

**Adverse events**

Nine (41%) dogs had no gastrointestinal or hematologic VCOG-CTCAEs recorded, including 2 of the 4 dogs treated with the COP protocol and 7 of the 18 dogs treated with the L-CHOP protocol. Hematologic VCOG-CTCAEs (ie, neutropenia) were recorded for 8 (36%) dogs, including 2 treated with the COP protocol (grade 1 adverse event in one dog and grade 4 in the other) and 6 treated with the L-CHOP protocol (grade 1 adverse event in 2 dogs, grade 3 in 1 dog, grade 4 in 2 dogs, and grade 5 in 1 dog [which had received an overdose]). Incidence of thrombocytopenia was not evaluated because platelet counts would have been unreliable owing to the artifactual influence of clumping. Gastrointestinal VCOG-CTCAEs were recorded for 11 (50%) dogs, including 1 treated with the COP protocol (grade 3 adverse event) and 10 treated with the L-CHOP protocol (grade 1 adverse event in 5 dogs and grade 2 in 5 dogs).

The overall rate of grade 3 or higher adverse events was 27% (6/22). Of these 6 dogs, 3 weighed ≥ 13 kg and 3 weighed < 13 kg.

The only death resulting from a VCOG-CTCAE involved a dog that received a 10-fold overdose of mitoxantrone. That dog became severely neutropenic and thrombocytopenic with bleeding and developed inappetence with grade 1 vomiting and melena. It was euthanized because of the poor prognosis while in complete remission.

**Duration of first remission**

Median duration of first remission for the 22 dogs was 181 days (95% CI, 117 to 245 days). Seven (32%) dogs died of unrelated causes during the first remission period.

The only factor significantly (P < 0.001) associated with duration of first remission was pretreatment anemia. For the 6 anemic dogs, median duration of first remission was 110 days (95% CI, 35 to 185 days; range, 34 to 185 days), and for the 15 dogs with a PCV within the reference range, the median value was 228 days (95% CI, 139 to 317 days; range, 22 to 707 days; Figure 1).

**Survival time**

By the time of analysis, 20 dogs had died and the other 2 were lost to follow-up at 155 and 139 days after treatment began. Of the 20 dogs that died, 12 (60%) dogs died of lymphoma (including 1 dog lost to follow-up while out of remission and the dog that died of mitoxantrone overdose, both categorized as having a lymphoma-related death). The dog with concurrent T-cell chronic lymphoid leukemia died while still in clinical remission from B-cell lymphoma.

![Figure 1](image-url)
Because necropsies were not performed, the cause of death for the remaining 7 dogs could not be ascribed with certainty given the available medical record information; this cause could have been lymphoma. All 7 dogs had died while in complete clinical remission and had completed the chemotherapy protocol. Two dogs were euthanized for unknown reasons at 15 and 17 years of age. Two dogs were euthanized for hind limb paresis (including the dog with preexisting lower motor neuron paresis). One dog was euthanized for renal failure, another for central neurologic signs and disorientation, and another for respiratory signs and vomiting.

Median survival time for all 22 dogs was 202 days (95% CI, 136 to 268 days; range, 22 to 1,063 days). One- and 2-year estimated survival rates for all dogs after chemotherapy began were 31% and 5%, respectively. Median survival time for the 4 dogs treated with the COP protocol was 181 days, and that for the 18 dogs treated with the L-CHOP protocol was 202 days ($P = 0.44$).

Of the putative prognostic factors evaluated, disease stage and substage and chemotherapy protocol (COP vs L-CHOP) had no significant association with survival time after chemotherapy began. Univariate analysis revealed 3 factors negatively associated with survival time (ie, associated with a briefer survival time): anemia (vs no anemia; $P = 0.02$), increasing body weight (as a continuous variable; $P = 0.04$), and body weight $\geq 13$ kg (vs $< 13$ kg; $P = 0.02$). On multivariate analysis controlling for anemia and body weight as a continuous or categorical variable, only body weight as a categorical variable retained a significant ($P = 0.02$) association with survival time.

For the 12 dogs weighing $\geq 13$ kg at initial diagnosis, median survival time was 114 days (95% CI, 82 to 200 days; range, 22 to 485 days), and for the other 10 dogs weighing $< 13$ kg, median survival time was 230 days (95% CI, 0 to 493 days; range, 139 to 1,063 days). The 1- and 2-year estimated survival rates for dogs $< 13$ kg were 50% and 12%, respectively (Figure 2).

**Discussion**

The strength of the human-animal bond reportedly increases the longer pets and owners live together. Consequently, very elderly dogs represent a population for which this bond is particularly strong, yet only anecdotal information exists regarding their tolerance for, and response to, antineoplastic treatment.

As is true of humans, most very elderly dogs with multicentric lymphoma in the present study had nonindolent B-cell lymphoma, accounting for 19 of the 20 dogs with a known lymphoma phenotype. Over the same period, the authors consulted on cases pertaining to 536 dogs with nonindolent B-cell lymphoma and 87 dogs with nonindolent T-cell lymphoma. Thus, very elderly dogs accounted for approximately 4% of canine DLBCL patients and 1% of canine T-cell lymphoma patients.

Without use of a standard chemotherapy protocol, the prognosis for the dogs in the present study appeared similar to that for younger patients, with a median survival time $< 4$ weeks for dogs receiving only prednisolone. Therefore, such protocols are likely to extend survival time in very elderly dogs, despite the comorbid diseases that can exist in this population.

As previously mentioned, a major limitation to treating very elderly dogs with lymphoma is the concern about chemotherapy-associated toxic effects, which may result in selection of a lower dosage. Indeed, our experience was that 4 owners in the present study chose a COP protocol for their dogs because they perceived it as a less risky, and not less expensive, treatment option. It was not possible to retrospectively determine the reasons for the choice of prednisolone rather than other options by owners, but similar concerns could have existed regarding the decision to treat or not treat.

Lower-intensity chemotherapy protocols involving no anthracycline (eg, doxorubicin) appear to result in fewer toxic effects in very elderly human DLBCL patients than higher intensity protocols, but survival times also decrease when such protocols are used. In the present study, only 4 dogs were treated with a protocol that included no anthracycline or anthracyclinedione (ie, the COP protocol), and these dogs had a median survival time of 181 days after chemotherapy began, whereas 18 dogs treated with the...
L-CHOP protocol had a median survival time of 202 days. Although the difference in survival times was not significant, all dogs that survived > 1 year were those that received the L-CHOP treatment. Numbers of VCOG-CTCAEs were too small to allow statistical comparison; however, these numbers were similar between the 2 chemotherapy protocols, and the most severe gastrointestinal adverse effect was in a dog receiving COP.

Diffuse large B-cell lymphoma is the cause of death in approximately 60% to 75% of human lymphoma patients with comorbidities, compared with < 15% for the comorbidities themselves.3,6 A similar pattern was observed in the dogs of the present study. Despite the pretreatment finding of renal dysfunction (evidenced by azotemia and a low urine specific gravity) in 5 dogs, renal failure was the cause of death for only 1 dog.

Anemia is reportedly more common in canine lymphoma patients > 10 years of age than in younger patients.20 Among very elderly dogs with multicentric lymphoma in the present study, dogs that were anemic before chemotherapy began had a briefer duration of first remission than nonanemic dogs. On the other hand, anemia had no association with survival time after controlling for other variables. In contrast, 2 other studies20,21 showed that anemic dogs with lymphoma had briefer survival times than nonanemic dogs with lymphoma, and 1 of these studies20 also showed that pretreatment anemia had no association with duration of remission.

Dogs with a lower body weight had longer median survival time in the present study than dogs with a higher body weight, and lower body weight is previously reported as a positive prognostic factor for dogs with lymphoma treated with chemotherapy.22–24 One suggested reason is that because drug doses are calculated on the basis of body surface area, smaller dogs receive a higher dose on a mg/kg basis.22–24 If that were true, then we might have expected a higher rate of toxic effects in dogs with lower body weights in the present study, but this was not apparent.

Weaknesses of the present study included the small number of dogs, which was unavoidable given that the very elderly dogs comprised < 5% of dogs with lymphoma in the study population. However, the included dogs represented the largest group of very elderly dogs with lymphoma to have been evaluated in a single study. In addition, the retrospective nature of the study design may have resulted in over- or underestimation of the rate and severity of adverse events, and clinical staging was not always complete or consistent. Cause of death could not be ascertained with certainty, given that necropsies were not performed; therefore, death from any cause was used as an endpoint.

Lymphoma was the most common cause of death of dogs in the present study, and the 7 dogs that received prednisolone rather than the COP or L-CHOP protocol (and were therefore excluded from analyses) had only a brief survival period. Clearly, advanced stage, nonindolent lymphoma is a life-threatening disease in very elderly dogs just as in younger dogs and cannot be expected to behave in a less biologically aggressive manner or to be overtaken in severity by other problems. However, survival time of dogs treated with a COP or L-CHOP protocol was substantially longer than that of dogs treated with only prednisolone and was not considerably briefer than reported survival times for the general population of dogs treated similarly for lymphoma (6.7 months in the present study vs 8.4 months25 and 10 months26 in other studies). One-year survival rates of 28% to 35% have been achieved with the L-CHOP protocol in other studies,3,27–29 and these rates are similar to the 31% estimated rate achieved with both the COP and L-CHOP protocols in the present study.

Observed toxic effects were acceptable and similar to those reported for younger dogs. The reported rate of grade 3 and 4 VCOG-CTCAEs with a similar CHOP-based protocol is 32%,25 and in another study,30 41% of treated dogs needed at least 1 dosage reduction because of toxic effects, compared with 27% of dogs in the present study. These data suggest that chemotherapy for lymphoma is beneficial and reasonably tolerated in very elderly dogs just as in younger dogs and need not be withheld on the basis of age alone.

### Acknowledgments

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### Footnotes

a. SPSS, version 10.0, IBM SPSS Inc, Chicago, Ill.

### References

8. Marchesi F, Cenfra N, Altomare L, et al. A retrospective study...


17. Veterinary Cooperative Oncology Group. Veterinary Cooperative Oncology Group—common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. Vet Comp Oncol 2016;14:417–446.


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### Appendix 1

The COP protocol used to treat very elderly dogs with multicentric lymphoma.

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• = Drug administered or CBC performed. — = Not applicable.  
+ = If neutrophil count < 3.0 X 10^9/L, then 1-week dose delay; if < 1.0 X 10^9/L, then prophylactic antimicrobials administered. ++ = If neutrophil count < 1.0 X 10^9/L, then prophylactic antimicrobials administered and future doses of the previously administered myelosuppressive drug decreased by 25%.

CTX = Cyclophosphamide (200 mg/m², IV) given with furosemide (2 to 4 mg/kg [0.9 to 1.8 mg/lb], IV). PRED = Prednisolone (40 mg/m², PO, q 24 h and tapered after last chemotherapy treatment, from weeks 19 through 22). VCR = Vincristine (0.75 mg/m², IV).

### Appendix 2

The L-CHOP protocol used to treat very elderly dogs with multicentric lymphoma.

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DOXO = Doxorubicin (1.0 mg/kg [0.45 mg/lb] or 30 mg/m²), substituted with mitoxantrone (MITO; 5.5 to 6.0 mg/m², IV) in dogs with cardiac abnormalities. L-ASP = l-asparaginase (10,000 U/m²; maximum dose, 10,000 U), PRED = Prednisolone (40 mg/m², PO, q 24 h and tapered over weeks 2 through 5).

See Appendix 1 for remainder of key.