

# CHOP chemotherapy for the treatment of canine multicentric T-cell lymphoma

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## Abstract

Dogs with multicentric T-cell lymphoma are commonly treated with CHOP chemotherapy protocols that include cyclophosphamide, doxorubicin, vincristine and prednisone. The purpose of this study was to evaluate the use of CHOP chemotherapy for dogs with multicentric T-cell lymphoma. Identification of prognostic factors in this specific subset of dogs was of secondary interest. Twenty-three out of 24 dogs responded to CHOP chemotherapy and these dogs remained on the protocol for a median of 146 days. No variable was associated with progression free survival (PFS) including stage, substage, hypercalcemia or radiographic evidence of a cranial mediastinal mass. The median overall survival time (OST) for all dogs was 235 days. Dogs that were thrombocytopenic at presentation experienced a significantly longer OST (323 versus 212 days,  $P = 0.01$ ).

## Keywords

canine, chemotherapy, CHOP, lymphoma, T cell

## Introduction

Doxorubicin-based chemotherapy protocols containing cyclophosphamide, vincristine and prednisone (CHOP), with or without L-asparaginase, are often recommended as first-line therapy for canine non-Hodgkin's lymphoma (NHL) patients regardless of immunophenotype. Whereas the B-cell immunophenotype is the most common form of canine NHL, approximately 10–38% of cases are of T-cell origin.<sup>1</sup> Although several morphological subtypes of canine T-cell lymphomas have been described, overall, the T-cell phenotype is associated with a poor prognosis when compared to B-cell NHL.<sup>2–7</sup>

Repeated studies have defined both clinical and molecular distinctions between B- and T-cell canine NHL; however, historical studies have not always separated analyses of B- and T-cell NHL patients.<sup>2–5,7–11</sup> While approximately 85% of canine NHL patients will present with multicentric

(stage III–V) disease, inclusion of canine patients with stage I–II, low-grade, or extranodal lymphoma may further confound the results of therapeutic efficacy studies.<sup>1</sup>

Combination chemotherapy with mechlorethamine, vincristine, procarbazine and prednisone (MOPP) for the treatment of dogs with T-cell (or hypercalcemic) NHL was recently reported.<sup>7</sup> Treatment with MOPP resulted in a 78% complete response (CR) rate with median progression free (PFS) and overall survival time (OST) of 189 and 270 days, respectively.<sup>12</sup> The PFS and OST of dogs that received MOPP therapy were numerically superior to most prior reports of dogs with confirmed T-cell lymphoma that were treated solely with CHOP-based chemotherapy (PFS 94–200 days and OST 120–239 days).<sup>3,5–7</sup> However, these historical studies were based on relatively few T-cell NHL dogs with unreported sites of involvement.

The purpose of this retrospective study was to evaluate the use of CHOP-based chemotherapy for first-line therapy of dogs with multicentric (stages III–V) T-cell NHL that were routinely

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staged. Evaluation of possible prognostic factors in this specific subset of dogs with generalized T-cell lymphoma was of secondary interest.

## Materials and methods

### Study population

Twenty-four dogs with T-cell lymphoma that were treated with a CHOP chemotherapy protocol at the University of California-Davis Veterinary Medical Teaching Hospital (UCD-VMTH) between January 2000 and January 2008 were retrospectively identified. Inclusion criteria were a cytological or histological diagnosis of intermediate- or high-grade lymphoma, confirmed T-cell immunophenotype, intent to treat with CHOP chemotherapy, and pre-treatment staging that included a complete blood count, serum chemistry panel, thoracic radiographs, abdominal ultrasound and a bone marrow aspirate. Dogs with stage I or stage II lymphoma, dogs with gastrointestinal or skin involvement and dogs with suspected low-grade lymphoma were excluded. Dogs with a history of prior chemotherapy or steroid treatment were also excluded.

### Diagnosis and staging

The diagnosis of NHL was made on cytopathological or histopathological evaluation of a lymph node in all cases. Immunoreactivity with CD3 antibody and lack of reactivity with CD79a constituted a diagnosis of T-cell NHL. Clinical stage was based on the World Health Organization (WHO) criteria for canine NHL<sup>1</sup>; however, splenic and liver aspirates were not routinely performed and therefore it was not possible to definitively differentiate stage III from stage IV disease in this population of patients. Two or three view thoracic radiographs were reviewed by a single board certified radiologist (SB). Thoracic radiographs were evaluated for enlargement of intrathoracic lymph nodes (sternal, mediastinal and tracheobronchial lymph nodes), changes of the lung pattern, or any other abnormalities.

### Response

A CR was considered as resolution of all clinically detectable diseases. A designation of no response or

partial response was determined based on the clinician's comments in the medical record, as lymph node measurements were not recorded in all cases.

### Statistical analyses

Complete and partial response rates were defined as the number of dogs experiencing respective remissions compared to the total number of dogs treated. PFS was defined as the time of first treatment until relapse. OST was defined as the time between first treatment and death. PFS and OST analyses were performed using the Kaplan-Meier product limit method. Dogs were censored if they were still in remission and alive at the time of analysis. Dogs lost to follow-up were censored at the last date of contact. Dogs were censored from analysis if the cause of death was confirmed to be unrelated to lymphoma on necropsy exam. The following variables were tested for their effect on PFS and OST by a log-rank test: stage V, bone marrow involvement, circulating blasts, substage, radiographic evidence of a cranial mediastinal mass, hypercalcemia, thrombocytopenia, leucopenia, weight, and use of vinblastine. A *P*-value  $\leq 0.05$  was considered statistically significant. A commercially available software program (Stata version 10.0, StataCorp LP, College Station, TX, USA) was used to perform statistical analyses.

## Results

### Treatment

Twenty-four dogs were included in this study. All dogs were treated with a 26-week CHOP chemotherapy protocol that included L-asparaginase (Table 1). Two of these 24 dogs were treated with maintenance therapy consisting of dactinomycin and leukeran after completion of the 26-week protocol. It is routine practice at the UCD-VMTH to substitute vinblastine for vincristine in patients that do not tolerate vincristine. In this regard, 8 out of 24 dogs (33%) received at least one dose of vinblastine during their CHOP protocol.

### Patient characteristics

Median age was 7 years (range 4–13 years). Breeds represented were mixed (6), Boxer (5), Golden Retriever (5), Labrador Retriever (1), Bulldog (1),

**Table 1.** CHOP-based chemotherapy treatment protocol

Protocol	Week																			
	0	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	24	26	
L-asparaginase (400 IU kg <sup>-1</sup> )	•																			
Vincristine (0.5–0.7 mg m <sup>-2</sup> IV)		•		•			•		•			•		•			•		•	
Cyclophosphamide (200–250 mg m <sup>-2</sup> IV or PO)			•					•					•					•		
Doxorubicin (30 mg m <sup>-2</sup> IV)					•					•						•				•
Prednisone (tapering dose)	•	•	•	•	•															

Weimeraner (2), Australian Cattle dog (1), Springer Spaniel (1), German Shepherd (1) and Cocker Spaniel (1). Thirteen dogs were neutered males, eight were spayed females and three were intact males. Nineteen dogs were diagnosed as having NHL based on cytological evaluation of lymph node aspirates, and the remaining five dogs were diagnosed based on histopathological evaluation of lymph node biopsies. T-cell NHL was diagnosed by immunocytochemistry in 21 dogs and immunohistochemistry in the remaining three dogs.

Fourteen dogs were categorized as having stage V disease. Eleven of these 14 dogs had evidence of bone marrow involvement, whereas 1 dog was classified as stage V based on ocular involvement. The additional two dogs classified as stage V disease were found to have circulating blasts on routine evaluation of their CBC, without demonstrable bone marrow involvement. In total, seven dogs were found to have circulating tumor cells on routine evaluation of the CBC. Thirteen dogs were of substage b and the remaining 11 dogs were considered substage a. Nine dogs were hypercalcemic on presentation. Fifteen dogs were suspected to have splenic involvement based on a mottled appearance of the spleen during abdominal ultrasound. The liver was suspected to be involved in 5 of 24 dogs, and 17 out of 24 dogs had intra-abdominal lymph node enlargement noted on the ultrasound report. Thirteen dogs had evidence of a cranial mediastinal mass on thoracic radiographs, 11 dogs had evidence of sternal lymph node enlargement and 9 dogs had evidence of tracheobronchial lymph node enlargement. Seven out of the 24 dogs had no radiographic evidence of intrathoracic lymph node enlargement. Seven dogs were thrombocytopenic on presentation (<150 000), and one dog had considerable anaemia (<35%).

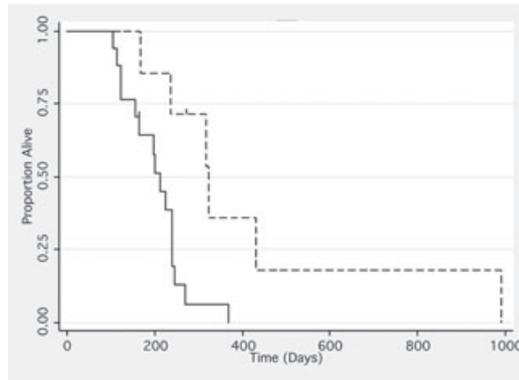
### Treatment response, survival and prognostic factors

The overall response rate in this population of dogs was 96%. Twenty-one out of 24 (88%) dogs had a CR to CHOP chemotherapy. Two dogs (8%) were designated as having a partial response, while one dog had no response (4%). Of the 23 dogs that experienced a response, the median time that they received CHOP-based chemotherapy was 146 days (95% CI 105–236 days). The median duration of CR was 104 days (95% CI 84–126 days). The two dogs with designated partial responses remained progression free on CHOP for 118 days and 133 days. None of the tested variables significantly affected PFS.

The OST for all dogs was 235 days (95% CI 167–244 days). Twenty-three of 24 dogs received non-standardized (non-CHOP) rescue chemotherapy protocols according to the clinician's and owner's preference. Rescue agents included CCNU (21 dogs), MOPP (5 dogs), DTIC (5 dogs), mitoxantrone (1 dog), cytosar (2 dogs) and toceranib (1 dog). Three dogs also underwent some form of palliative radiation therapy and two dogs underwent surgical palliation. OST from the start of non-CHOP rescue therapy was 66 days. No deaths were confirmed to be from causes unrelated to lymphoma. Dogs that were thrombocytopenic at presentation experienced a significantly longer median OST (323 versus 212 days,  $P = 0.01$ ) (Fig. 1). No other variables were significantly associated with OST.

### Discussion

The purpose of this study was to evaluate the use of CHOP chemotherapy in dogs with multicentric T-cell NHL. A secondary goal was to evaluate



**Figure 1.** Kaplan-Meier curve of OST for dogs with or without thrombocytopenia at the time of NHL diagnosis. Dogs that were thrombocytopenic at presentation experienced a significantly longer median OST (323 days versus 212 days,  $P = 0.01$ ). Tick marks indicate censored cases.

prognostic factors associated with PFS and OST in this specific subset of patients. In dogs with multicentric NHL, we found that the T-cell phenotype was associated with a high initial response rate but that the response was of limited duration (PFS 104 days). No prognostic factor was found to be associated with PFS.

Several variations of CHOP chemotherapy have been published for dogs with NHL, but these studies have included very few confirmed cases of T-cell NHL.<sup>3–7,13,14</sup> One large series examined the PFS and OST of 175 dogs with NHL; 38 of them were determined to be of T-cell origin.<sup>4</sup> The T-cell phenotype was associated with a poor prognosis (PFS 52 days, OST 160 days) when compared with B-cell NHL patients (PFS 153 days, OST 330 days); however, chemotherapy was not standardized and not all patients received CHOP chemotherapy.<sup>4</sup> PFS and OST were reported to be 96 days and 159 days, respectively, in 10 cases of canine T-cell NHL that received CHOP chemotherapy.<sup>3</sup> It was not noted whether only multicentric NHL patients were included; however, inclusion was limited to dogs that had intermediate- or high-grade NHL and advanced clinical stage.<sup>3</sup> Evaluation of a high-dose CHOP protocol in nine dogs with confirmed T-cell NHL reported a median first remission of 150 days and an OST of 120 days.<sup>6</sup> Although not specified by immunophenotype, approximately 30% of the dogs evaluated in the

high-dose study had received some form of prior chemotherapy.<sup>6</sup> Two additional studies reported median disease free intervals (DFIs) of 94 days ( $n = 5$ ) and 200 days ( $n = 5$ ) in dogs with T-cell NHL receiving CHOP chemotherapy protocols.<sup>5,7</sup> Lastly, two studies evaluating CHOP chemotherapy in dogs with suspected T-cell NHL (based on the presence of hypercalcemia) reported PFS times of 124 ( $n = 5$ ) and 139 days ( $n = 15$ ).<sup>13,14</sup> A summary of previously reported CHOP chemotherapy for dogs with T-cell NHL is presented in Table 2.

Combination chemotherapy with MOPP for the treatment of dogs with T-cell NHL was recently reported in 50 dogs.<sup>12</sup> Treatment with MOPP resulted in a 78% CR rate with median PFS and OST of 189 days and 270 days, respectively. The PFS and OST of dogs that received MOPP therapy were numerically superior to most reports of T-cell NHL dogs that were treated with CHOP-based chemotherapy, but case selection and treatment were not always consistent within and between cited studies. This makes conclusions based on comparisons between the MOPP study and historical CHOP studies difficult.

In dogs with multicentric T-cell NHL that received CHOP, we report a complete and overall response rate (ORR) of 88% and 96%, respectively. These response rates are quite similar to response rates for dogs with T-cell NHL that received MOPP (78% CR, 98% ORR).<sup>12</sup> While these response rates seem higher than expected based on historical reports, we feel that the high response rates are likely a result of case selection. Exclusion of dogs with gastrointestinal or skin involvement likely excluded dogs that might be expected to respond poorly. It is also possible that induction with a single dose

**Table 2.** CHOP therapy for dogs with T-cell or hypercalcemic NHL

Number of dogs	PFS (days)	OST (days)	Reference
<i>CD3+, T-cell NHL</i>			
10	96	159	Vail <sup>3</sup>
9	150	120	Chun <sup>6</sup>
5	94	239	Siedlecki <sup>7</sup>
5	200	Not reported	Simon <sup>5</sup>
24	104	235	Current study
<i>Hypercalcemic NHL</i>			
15	139	Not reported	Kaiser <sup>13</sup>
5	124	240	Garrett <sup>14</sup>

of L-asparaginase may have contributed to such high response rates, because dogs with T-cell NHL in this report and dogs treated with MOPP both received a single dose of L-asparaginase initially. We feel that the previous scenario is unlikely based on the fact that L-asparaginase has not been shown to influence ORR in previous reports of dogs with NHL.<sup>15,16</sup> Nevertheless, the effects of L-asparaginase for dogs with T-cell NHL remains unknown.

The PFS (104 days) was within the range of previous CHOP chemotherapy reports. At first glance, the PFS of dogs receiving CHOP treatment appears inferior to dogs treated with MOPP in the Brodsky study (189 days); however, we defined PFS as the time from initiation of treatment until first relapse. PFS in the MOPP study was defined as the time from initiation of treatment until evidence of progressive disease that was unresponsive to MOPP. Using a similar definition of PFS (unresponsive to all drugs in CHOP chemotherapy), the median PFS in our study was 146 days. It is anticipated that uniform adoption of the recently published Veterinary Cooperative Oncology Group (VCOG) guidelines will allow more consistent comparisons in the future.<sup>17</sup>

The OST of dogs in our study was 235 days, and not that dissimilar to the 270 days reported for dogs treated with MOPP therapy. Treatment with MOPP resulted in 25% of dogs alive at 939 days, whereas our case series had a 14% and 5% survival rate at 1 and 2 years, respectively. The case selection in our study was slightly more rigorous than the previous MOPP study because we included only patients with multicentric NHL and positive CD3 immunostaining. We also excluded stage I–II disease, and dogs with suspected or confirmed low-grade lymphoma. It is not known whether case selection may account for the differences in reported long-term survivals. Similarly, reporting only dogs that underwent routine staging may have also biased the patient population towards higher stage disease.

Unfortunately, the cost associated with chemotherapy can be prohibitive for pet owners seeking treatment for their pets. At UC Davis, a recommendation for MOPP chemotherapy carries a substantial increase in drug costs when compared to CHOP therapy. However, costs associated with

chemotherapy and chemotherapy administration are likely to vary greatly depending on both the institution and the availability of drugs.

Hypercalcemia, substage, and presence of a cranial mediastinal mass have all been reported as negative prognostic factors in dogs with NHL.<sup>14,18</sup> These factors are commonly associated with the T-cell phenotype, and to date, very little information exists regarding the prognostic value of such factors for dogs with multicentric T-cell NHL. Interestingly, no prognostic factors were identified in dogs with suspected T-cell NHL that underwent treatment with MOPP. Our results are similar. Specifically, hypercalcemia, presence of a cranial mediastinal mass, and clinical sub-stage were not significantly associated with PFS or OST in dogs with multicentric T-cell NHL.

Thrombocytopenia was found to be significantly associated with an increased OST. Thrombocytopenia has previously been identified as a positive prognostic factor for OST in dogs with NHL that received CHOP chemotherapy.<sup>14</sup> In contrast, two separate studies report that pre-treatment thrombocytopenia was associated with shorter remission durations in dogs that achieved a CR in response to VELCAP.<sup>18,19</sup> Unfortunately, immunologic phenotyping was not performed in any of the prior studies. It is possible that the prognostic significance of thrombocytopenia may be dependent on immunophenotype. It is also possible that thrombocytopenia may be associated with specific morphological subtypes of T-cell NHL. The finding that thrombocytopenia is a positive prognostic factor for survival in dogs with T-cell NHL should be interpreted with caution until it can be confirmed in a larger population of dogs.

While this study examined a specific sub-set of dogs with multicentric T-cell NHL that received CHOP chemotherapy, it has several limitations. In addition to its retrospective nature, very few dogs had correlative histopathologic diagnoses. Not all canine T-cell NHL's carry a similar prognosis, and the exclusion of the morphological subtype in this study represents a significant gap when evaluating treatment efficacy.<sup>2</sup> Furthermore, while OST is reported in our study, OST is dependent upon many variables including rescue therapy and euthanasia. A recently published VCOG consensus

document has advocated the use of PFS (using RECIST criteria) for more consistent evaluation of future canine NHL studies.<sup>17</sup> Because of the retrospective nature of this study, RECIST criteria were not used. Inclusion of OST in this particular study was felt appropriate given the paucity of data on CHOP chemotherapy in this specific subset of dogs with confirmed multicentric T-cell NHL.

Based on the results of this retrospective analysis, several questions remain unanswered. PFS in this study is numerically shorter than the PFS reported with MOPP but the method of determining PFS is not identical among these studies. When we used a similar method of determining PFS, dogs treated with CHOP had a PFS of 146 days (95% CI, 105–236 days). Overlap of confidence intervals would indicate that there is likely no difference in PFS or OST between dogs treated with CHOP and those treated with MOPP.<sup>12</sup> Based on these data, a prospective, randomized clinical trial would be required to determine if MOPP provides an overall long-term survival benefit. Because canine T-cell NHL is a heterogeneous disease that carries a variable prognosis, further comparisons should include evaluation of histopathology in addition to confirmation of T-cell origin.<sup>2</sup> In conclusion, for dogs with multicentric T-cell NHL, clients who are unable to afford treatment costs associated with MOPP therapy can still be well served with CHOP therapy.

## References

1. Withrow SJ and Vail DM. *Withrow and MacEwen's Small Animal Clinical Oncology*, 4<sup>th</sup> edn., Edinburgh, Elsevier Saunders, 2007.
2. Ponce F, Magnol J, Ledieu D, Marchal T, Turinelli V, Chalvet-Monfray K, Fournel-Fleury C. Prognostic significance of morphological subtypes in canine malignant lymphomas during chemotherapy. *Veterinary Journal* 2004; **167**: 158–166.
3. Vail DM, Kisseberth WC, Obradovich JE, Moore FM, London CA, MacEwen EG, Ritter MA. Assessment of potential doubling time (Tpot), argyrophilic nucleolar organizer regions (AgNOR), and proliferating cell nuclear antigen (PCNA) as predictors of therapy response in canine non-Hodgkin's lymphoma. *Experimental Hematology* 1996; **24**: 807–815.
4. Ruslander DA, Gebhard DH, Tompkins MB, Grindem CB and Page RL. Immunophenotypic characterization of canine lymphoproliferative disorders. *In Vivo* 1997; **11**: 169–172.
5. Simon D, Nolte I, Eberle N, Abbrederis N, Killich M and Hirschberger J. Treatment of dogs with lymphoma using a 12-week, maintenance-free combination chemotherapy protocol. *Journal of Veterinary Internal Medicine* 2006; **20**: 948–954.
6. Chun R, Garrett LD and Vail DM. Evaluation of a high-dose chemotherapy protocol with no maintenance therapy for dogs with lymphoma. *Journal of Veterinary Internal Medicine* 2000; **14**: 120–124.
7. Siedlecki CT, Kass PH, Jakubiak MJ, Dank G, Lyons J and Kent MS. Evaluation of an actinomycin-D-containing combination chemotherapy protocol with extended maintenance therapy for canine lymphoma. *The Canadian Veterinary Journal* 2006; **47**: 52–59.
8. Rebhun RB, Lana SE, Ehrhart EJ, Charles JB and Thamm DH. Comparative analysis of survivin expression in untreated and relapsed canine lymphoma. *Journal of Veterinary Internal Medicine* 2008; **22**: 989–995.
9. Modiano JF, Breen M, Burnett RC, Parker HG, Inusah S, Thomas R, Avery PR, Lindblad-Toh K, Ostrander EA, Cutter GC, Avery AC. Distinct B-cell and T-cell lymphoproliferative disease prevalence among dog breeds indicates heritable risk. *Cancer Research* 2005; **65**: 5654–5661.
10. Fosmire SP, Thomas R, Jubala CM, Wojcieszyn JW, Valli VE, Getzy DM, Smith TL, Gardner LA, Ritt MG, Bell JS, Freeman KP, Greenfield BE, Lana SE, Kisseberth WC, Helfand SC, Cutter GR, Breen M, Modiano JF. Inactivation of the p16 cyclin-dependent kinase inhibitor in high-grade canine non-Hodgkin's T-cell lymphoma. *Veterinary Pathology* 2007; **44**: 467–478.
11. Thomas R, Smith KC, Ostrander EA, Galibert F and Breen M. Chromosome aberrations in canine multicentric lymphomas detected with comparative genomic hybridisation and a panel of single locus probes. *British Journal of Cancer* 2003; **89**: 1530–1537.
12. Brodsky EM, Maudlin GN, Lachowicz JL and Post GS. Asparaginase and MOPP treatment of dogs with lymphoma. *Journal of Veterinary Internal Medicine* 2009; **23**: 578–584.
13. Kaiser CI, Fidel JL, Roos M and Kaser-Hotz B. Reevaluation of the University of Wisconsin 2-year protocol for treating canine lymphosarcoma.

- Journal of the American Animal Hospital Association* 2007; **43**: 85–92.
14. Garrett LD, Thamm DH, Chun R, Dudley R and Vail DM. Evaluation of a 6-month chemotherapy protocol with no maintenance therapy for dogs with lymphoma. *Journal of Veterinary Internal Medicine* 2002; **16**: 704–709.
  15. Jeffreys A, Knapp D, Carlton W, Thomas R, Bonney P, Degortari A, Lucroy M. Influence of asparaginase on a combination chemotherapy protocol for canine multicentric lymphoma. *Journal of the American Animal Hospital Association* 2005; **41**: 221–226.
  16. MacDonald V, Thamm D, Kurzman I, Turek M and Vail D. Does L-asparaginase influence efficacy or toxicity when added to a standard CHOP protocol for dogs with lymphoma? *Journal of Veterinary Internal Medicine* 2005; **19**: 732–736.
  17. Vail D, Michels G, Khanna C, Selting K and London C. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)–a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Veterinary and Comparative Oncology* 2010; **8**: 28–37.
  18. Moore AS, Cotter SM, Rand WM, Wood CA, Williams LE, London CA, Frimberger AE, L’Heureux DA. Evaluation of a discontinuous treatment protocol (VELCAP-S) for canine lymphoma. *Journal of Veterinary Internal Medicine* 2001; **15**: 348–354.
  19. Zemmann BI, Moore AS, Rand WM, Mason G, Ruslander DM, Frimberger AE, Wood CA, L’Heureux DA, Gliatto J, Cotter SM. A combination chemotherapy protocol (VELCAP-L) for dogs with lymphoma. *Journal of Veterinary Internal Medicine* 1998; **12**: 465–470.