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Evaluation of a Discontinuous Treatment Protocol (VELCAP-S) for Canine Lymphoma

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Eighty-two dogs with lymphoma received a single 15-week course of chemotherapy, after which treatment was ceased until relapse. Fifty-six dogs (68%) achieved complete remission for a median 1st remission duration of 20 weeks. Forty-eight dogs relapsed, of which 30 repeated the induction cycle. In 22 of these dogs, 1st remission had been short, and they received maintenance chemotherapy; the other 8 dogs received 2 or 3 cycles of induction chemotherapy. Second remission rate for these 30 dogs was 87% (26 dogs). Overall disease control for the 38 dogs that remained on protocol was 44 weeks, which was not markedly shorter than for dogs treated with a previously reported protocol in which maintenance chemotherapy was instituted in all dogs after an identical 1st induction (VELCAP-L). Dogs that were febrile and dogs that were dyspneic were less likely to achieve a complete remission to induction chemotherapy. Of dogs that achieved a complete remission, those that were thrombocytopenic at entry had a shorter 1st remission, and dogs that were anorexic at entry had shorter overall disease control. There was a correlation between 1st remission duration and length of any subsequent remission obtained. The incidence of toxicity was high, particularly after the combination of doxorubicin and vincristine. Dose reductions because of toxicity did not markedly reduce remission duration. We conclude that discontinuous chemotherapy may reduce patient visits in a small number of patients because of long-term disease control. Delaying maintenance chemotherapy until after 2nd remission is achieved does not markedly affect overall disease control.

Key words: Cancer; Chemotherapy; Dog.

Combination chemotherapy is a successful treatment strategy for canine lymphoma. Protocols utilizing the 5 most active drugs (doxorubicin, vincristine, cyclophosphamide, L-asparaginase, and prednisone) provide high response rates and remission durations of 12 months or more.[1–5] Despite differences in these protocols, their overall effectiveness does not vary greatly, and it is unlikely that further minor manipulations in scheduling will provide major advances in response rate or duration.

Because palliation, rather than cure, is a major goal of chemotherapy in veterinary oncology, there has been recent interest in developing protocols that reduce the number of patient visits as well as cost and toxicity of treatment. The use of short-term chemotherapy given in pulse doses may provide remission durations similar to long-term maintenance chemotherapy.[6,7]

In human oncology, the strategy of using noncross resistant chemotherapeutics for maintenance has been helpful in preventing relapses in childhood acute lymphoid leukemias but is felt to be ineffective in the treatment of non-Hodgkin's lymphoma.[8] It has also been shown that human patients with Hodgkin's disease who relapse after having achieved a complete remission are more likely to reattain a complete remission than newly diagnosed patients with same stage of disease.[9] This implies that discontinuous chemotherapy may provide a remission duration similar to long-term maintenance chemotherapy at a lower dose intensity.

Therefore, to examine the utility of discontinuous chemotherapy for veterinary practice, we evaluated a protocol based on a 15-week induction protocol (VELCAP-S).

Materials and Methods

Criteria for Selection of Dogs

The medical records of 90 dogs treated for lymphoma at Tufts University School of Veterinary Medicine between June 1994 and April 1996 were reviewed. Eight of these dogs received other chemotherapeutic agents or had mycosis fungoides and were excluded from analysis. Twenty-one dogs had received prednisone before starting chemotherapy, and these dogs were included in the study. Records from a total of 82 dogs that received at least the 1st treatment of VELCAP-S were available for analysis.

Chemotherapy Protocol

The doses and scheduling for VELCAP-S are provided in Table 1. After completion of 12 weeks of chemotherapy, the prednisone dose was reduced over 3 weeks, halving the dosage each week until, by week 15, all treatment was ceased. Dogs then received a complete physical examination every month until the lymphoma again became clinically apparent (relapse). If the period from the last chemotherapy administration to relapse (period off chemotherapy, not remission) was $>$16 weeks (duration of the induction period), the dog was eligible to receive a 2nd induction course of chemotherapy, and this sequence was followed until the period off chemotherapy was $<$16 weeks in duration. If this time period was $<$16 weeks, the dog was treated with an identical induction, then received continued maintenance chemotherapy as has been described (see Table 2).[5] Any dosage reductions were maintained in all subsequent chemotherapy administrations.

Dogs that received all drugs on schedule and at full dosage were considered to have received the intended dose intensity for the protocol. Dogs that had dose reductions or treatment delays had a lower than intended dose intensity. This relative dose intensity was calculated as a percentage for each drug, and the sum of all relative dose intensities for the 4 drugs was divided by the number of drugs to provide a calculated "received dose intensity."[10] The received dose intensity was calculated only for dogs that completed the initial 15 weeks of the VELCAP-S protocol.

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Table 1. Schematic for administration of chemotherapy drugs in VELCAP-S induction for canine lymphoma.[a]

	VELCAP-S Induction											
Weeks	1	2	3	4	5	6	7	8	9	10	11	12
PRED	[	→										
DOX		●		●								
VCR	●	●	●				●					●
CTX							●					●
L-ASP							●	●	●			

[a] PRED, prednisone 40 mg/m² q24h PO for 7 days, then every alternate day. From week 12, taper by reducing dose by ½ each week until week 15; DOX, doxorubicin 25 mg/m² IV; VCR, vincristine 0.75 mg/m² IV; CTX, cyclophosphamide 250 mg/m² PO. If cystitis occurs, substitute with chlorambucil at 15 mg/m² PO daily for 4 consecutive days on same schedule; L-ASP, L-asparaginase 10,000 IU/m² IM, to a maximum dose of 10,000 IU per administration. If relapse occurs >16 weeks after last treatment, repeat VELCAP-S (induction). If relapse occurs <16 weeks after last treatment, use VELCAP-S (maintenance).

Diagnosis and Staging

Of the 82 dogs, the diagnosis of lymphoma was made on biopsy of lymph node or extranodal mass in 64 dogs, by aspiration cytology of lymph node or extranodal mass in 16 dogs, and by bone marrow aspiration cytology in 2 dogs. Forty-five biopsy specimens were available for histologic review and were classified as immunoblastic or nonimmunoblastic.

All dogs were clinically staged at diagnosis by means of a modification of the World Health Organization (WHO) 5-stage criteria for canine lymphoma.[11] In addition, dogs were assigned to substage categories of ''a'' (without constitutional clinical signs) or ''b'' (defined as hypercalcemia, gastrointestinal, or respiratory signs, fever [temperature >102.5°F], hyphema, or uveitis). Pretreatment evaluation included a CBC, serum chemistry profile, urinalysis, and thoracic radiographs. Bone marrow aspiration was performed if neutropenia or circulating lymphoblasts were detected. Abdominal radiography or ultrasonography was performed when clinically indicated. Because not all dogs were staged in a standard manner, it is likely that some dogs with more advanced lymphoma (stage V) may been classified as less advanced.

Assessment of Response

Any dog entered into the protocol was included in the analysis. Dogs that received only 1 treatment and were euthanized were still considered to have intent to treat and were evaluated despite not completing the induction protocol.

Complete remission was defined as the disappearance of all clinical evidence of disease as evidenced by physical examination, radiography, or ultrasonography within the chemotherapy period. No response signified a transient remission (as defined above) for less than 3 weeks, any response less than a complete remission, or progression of measurable disease during treatment.

Overall survival was not evaluated because of the confounding influences of euthanasia and the owner's willingness to pursue other forms of treatment.

Assessment of Toxicity

Only toxicoses severe enough to necessitate dose reduction or cessation of a drug were evaluated. Toxicoses included neutropenia below 1,000 cells/μL with or without signs of fever, gastrointestinal signs necessitating hospitalization, sterile hemorrhagic cystitis, reduction in cardiac contractility as assessed by ultrasonography, allergic reaction to L-asparaginase, and other clinical signs that were determined to be detrimental to quality of life (eg, psychosis, polyphagia, or hind limb weakness from prednisone).

Only dogs receiving the drug were included in analysis of that drug's toxicity. For example, if a dog died or treatment was ceased before week 7 of treatment, the dog was not included in toxicity analysis for cyclophosphamide or L-asparaginase. Because the VELCAP-S protocol uses drug combinations, the true cause of a toxicity was difficult to ascribe to an individual drug. Under these circumstances, the most myelosuppressive or most likely drug to cause the toxicity was reduced in dosage by 25% for all subsequent administrations (ie, after doxorubicin and vincristine, myelosuppression mandated a 25% reduction in the dose of doxorubicin).

Prognostic Factors

Two endpoints for response in this study were evaluated for prognostic significance. The length of 1st remission duration was defined as the period of time (in weeks) from the time at which a dog achieved complete remission until the 1st objective evidence of relapse.

Overall protocol remission duration was defined as the time from which a dog 1st achieved complete remission until relapse, which did not respond to subsequent VELCAP-S administration. The overall protocol remission duration therefore may include 1 or more clinical relapses.

The clinical factors evaluated for potential prognostic significance as to the likelihood of a dog entering complete remission or for developing toxicoses included: age, weight, gender, clinical substage, presence of a mediastinal mass, signs of respiratory difficulty, hypercalcemia, anemia, thrombocytopenia, serum concentrations of alanine transferase, alkaline phosphatase and bilirubin, prior treatment with prednisone, and whether the dog exhibited signs of drug toxicity during chemotherapy.

Table 2. Schematic for adminstration of chemotherapy drugs in VELCAP-S maintenance phase for canine lymphoma. Maintenance chemotherapy was used if the first remission duration was <16 weeks from last inducation chemotherapy.[a]

	VELCAP-S Maintenance																	
Weeks	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	25	27
PRED	Daily [	→			Alternate day	→												
DOX		●		●										●				●
VCR	●	●	●				●					●	●	●	●			●
CTX							●					●	●		●	●		
L-ASP							●	●	●							●	●	

[a] PRED, prednisone 40 mg/m² q24h PO for 7 days, then every alternate day; DOX, doxorubicin 25 mg/m² IV; VCR, vincristine 0.75 mg/m² IV; CTX, cyclophosphamide 250 mg/m² PO. If cystitis occurs, substitute with chlorambucil at 15 mg/m² PO daily for 4 consecutive days on same schedule; L-ASP, L-asparaginase 10,000 IU/m² IM, to a maximum dose of 10,000 IU per administration. From week 30, repeat weeks 12–18 every 9 weeks until week 52, then treatments are given every 4 weeks to week 78.

The clinical factors evaluated for prognostic significance, as to the length of both 1st remission and overall protocol remission durations, included those factors listed above, as well as the number of weeks taken to achieve complete remission and received dose intensity for the induction period of 5 weeks. In addition, the influence of 1st remission duration on overall protocol remission duration was evaluated.

Statistical Methods

Univariate analysis of the unadjusted association between each prognostic factor and whether a dog achieved complete remission was performed by means of chi-squared statistics for categorical variables and the Student's *t*-test for continuous variables. Statistical significance was defined as $P < .05$. Any factor significant at the .05 concentration was included in logistic regression multivariate analysis. The prevalence of the 4 most common purebreds was compared with the hospital patient population for the same time period by means of Fisher's exact 2-tailed test.

Remission (1st remission duration and overall protocol remission duration) curves were estimated by Kaplan-Meier statistics. Four dogs were censored from remission (1st remission duration) analysis because they were still in remission. Three dogs that died due to drug toxicity were accepted as reaching an endpoint. Twenty-six dogs were censored from overall protocol remission duration analysis: the 4 above, plus a further 4 dogs still in remission and 18 dogs that received other chemotherapy (6 dogs) or no further chemotherapy (12 dogs) on relapse after achieving a complete remission to induction treatment. Two dogs that died of unrelated disease in complete remission were accepted as reaching an endpoint. The association between each prognostic factor and 1st remission duration and overall protocol remission duration was examined by means of Cox regression analysis. Kaplan-Meier survival statistics were used to compare overall protocol remission duration with remissions for a previously reported protocol VELCAP-L.[5] The Pearson correlation test was used to assess the association between 1st remission duration and overall protocol remission duration in VELCAP-S.

The association between the primary indicators of toxicity and potential risk factors was tested by the chi-squared (Fisher exact) test for the categorical variables and the Student's *t*-test for the continuous variables.

Results

Population Characteristics

Twenty-two breeds of dogs entered into treatment on this protocol. The most commonly treated breeds were Golden Retrievers (22%), mixed breed dogs (12%), Labrador Retrievers (12%), Rottweilers (10%), and German Shepherds (5%). Comparison of the top 4 purebreds with the hospital population showed that Golden Retrievers (RR = 2.8; 95% CI = 1.8–4.2; $P = .0003$) and Rottweilers (RR = 2.5; 95% CI = 1.3–4.9; $P = .036$) were at higher risk for developing lymphoma when compared with the hospital population.

The median age of all dogs was 7 years (range, 1–15 years). Forty-two dogs were male (24 castrated, 18 intact), and 40 dogs were female (35 spayed, 5 intact). The median weight was 31 kg (range, 5.9–65.5 kg).

Clinical Staging

The majority of dogs were in clinical stages I–III. Three dogs (4%) were classified as stage I, 5 dogs (6%) as stage II, 52 dogs (63%) as stage III, 12 dogs (15%) as stage IV, and 10 dogs (12%) as stage V. Bone marrow aspirates were not performed on all dogs, so the number of stage V dogs may be higher than stated. Although most dogs (50) were classified as substage ''a,'' 32 dogs had 1 or more constitutive signs (substage ''b''). The most common clinical signs of illness at presentation were vomiting (13 dogs), dyspnea (10 dogs), and diarrhea (7 dogs).

Eleven dogs had hypercalcemia on serum chemistry, and 7 of these dogs also had a mediastinal mass on thoracic radiography. One further dog had evidence of a mediastinal mass without hypercalcemia.

Twenty-seven dogs were anemic (hematocrit <37%, erythrocyte count $<5.6 \times 10^6/\mu L$, or both). Nineteen dogs were thrombocytopenic (platelet count below 200,000/μL), with a median of $111 \times 10^3/\mu L$ (range, 18×10^3–196×10^3); 16 of these 19 dogs were also anemic.

Histologic grading was restricted to immunoblastic and nonimmunoblastic subtypes. Five (11%) of the 45 available specimens were characterized as immunoblastic.

Response Criteria

Fifty-six of 82 dogs (68%) that entered into the VELCAP-S protocol obtained a complete remission. Twenty-four of the 26 dogs that did not achieve complete remission received fewer than 3 treatments. Of these dogs, 2 were classified as stage I (both b), 8 as stage III (4 a, 4 b), 6 as stage IV (4 a, 2 b), and 6 as stage V (all b). From these 24, 2 dogs were lost to follow-up, and 22 were euthanized or died due to toxicity or owners' decisions (because of poor prognosis).

The median dose intensity for the 56 dogs was 96% (range, 80–100%); 31 dogs received less than 100% dose intensity.

Duration of therapy until the 1st day of complete remission was variable. The average time until 1st day of complete remission was 2.2 weeks. For the 56 dogs that achieved complete remission, 12 dogs (21%) were in complete remission after 1 week, 29 dogs (52%) after 2 weeks, 41 (73%) after 3 weeks, 43 (77%) after 4 weeks, 47 (84%) after 5 weeks, 49 (88%) after 6 weeks, and 51 (91%) after 7 weeks, and all dogs that ultimately attained complete remission were in remission after 8 weeks of treatment.

Of the factors evaluated for potential prognostic value as to the likelihood of a dog entering remission, both stage and substage were significant. Dogs in lower stages and dogs in substage a were more likely to enter remission: stages I and II, 6 of 8; stage III, 41 of 52; and stages IV and V, 9 of 22; substage a, 42 of 50; and substage b, 14 of 32. Additionally, dogs that were anorexic, dyspneic, or had a fever on presentation were less likely to achieve remission.

Multiple logistic regression of the possible prognostic factors of stage, substage, anorexia, fever, and dyspnea showed that only fever ($P = .001$) and dyspnea ($P = .01$) were independent prognostic variables.

1st Remission Duration

For the 56 dogs that achieved complete remission, the median 1st remission duration was 20 weeks. Three dogs died due to drug toxicity after the 2nd week of chemotherapy; they were in complete remission, and the durations of

their 1st remission were 0, 0, and 1 week, respectively. Four dogs were still in 1st remission at 90, 122, 129, and 153 weeks, and 1 dog was euthanized because of an unrelated disease in 1st remission at 97 weeks. Of the factors evaluated for potential prognostic significance for the length of 1st remission, 4 were identified: these factors were anorexia, polyuria/polydypsia, thrombocytopenia, and hypercalcemia. Cox regression of 1st remission duration on these 4 factors showed only thrombocytopenia ($P = .026$) to be an independent predictor for length of 1st remission. Dogs that were thrombocytopenic at entry had a median 1st remission duration of 15 weeks compared with 22 weeks for dogs without thrombocytopenia.

Overall Protocol Remission Duration

Of the 56 dogs that achieved complete remission, 48 (90%) relapsed. Thirty dogs repeated the induction protocol, and the 2nd remission rate for these 30 dogs was 87% (26 dogs). The time from last treatment to relapse was >16 weeks for 8 dogs. These 8 dogs repeated only the 12-week induction protocol for 1 further cycle (4 dogs) or 2 further cycles (4 dogs). Of the 8 dogs repeating the induction after 1st relapse, 7 dogs (88%) achieved a complete remission; of the 4 dogs repeating the induction after 2nd relapse, 2 dogs (50%) achieved a complete remission. For 22 of 48 dogs, the time from last treatment to relapse was less than 16 weeks. These dogs received induction followed by maintenance chemotherapy, and 19 of 22 (86%) achieved complete remission. For the 30 dogs that continued on the protocol, their subsequent remission time was a median of 22 weeks (range, 0–72 weeks; mean, 27 weeks). Of the 18 remaining dogs, 3 dogs received only vincristine, cyclophosphamide, and prednisone because of the owner's financial concerns, and 3 dogs received doxorubicin alone (2 dogs) or L-asparaginase alone (1 dog). Twelve dogs received no further chemotherapy on relapse because of the owner's reluctance to pursue further treatment. These 18 dogs were censored from statistical evaluation of overall protocol remission duration.

The median overall protocol remission duration was 44 weeks. At the conclusion of this study, 8 dogs were still in remission—the 4 dogs still in 1st remission and 4 additional dogs in remission at 76, 88, 89, and 97 weeks. Another dog died in remission, due to unrelated causes, 83 weeks after 1st achieving complete remission, having received 3 induction cycles.

Of the factors evaluated for potential prognostic significance for length of overall protocol remission duration, 4 factors were identified. Dogs that were anorexia, hypercalcemic, or had a mediastinal mass were found to have shorter overall protocol remission duration. In addition, the 1st remission duration was positively correlated with overall protocol remission duration.

Cox regression showed anorexia ($P = .036$) and 1st remission duration ($P = .0002$) to be independent predictors of overall protocol remission duration. Dogs that were anorexic had a median overall protocol remission duration of 20 weeks, whereas dogs that had a normal appetite had a median overall protocol remission duration of 52 weeks (see Fig 1). Correlation of 1st remission duration and overall protocol remission duration was significant at the $P = .01$ concentration by the Pearson correlation test. A similarly significant correlation was also seen between 1st remission duration and subsequent remission duration (overall protocol remission duration minus 1st remission duration) at the $P = .01$ concentration.

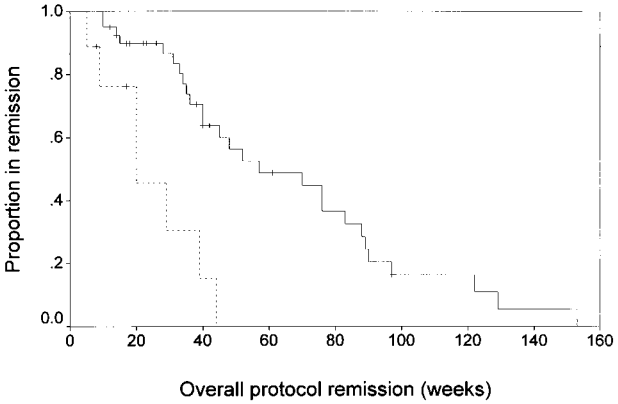

Fig 1. Overall protocol remission duration. Anorexia at the time of presentation was a marked predictor of overall protocol remission duration for dogs that achieved remission. The dashed line indicates anorexic dogs (median, 20 weeks; 10 dogs), and the solid line, dogs with normal appetite (median, 52 weeks; 46 dogs). The difference was significant ($P = .036$). Vertical lines denote 18 dogs that were censored from analysis (see text).

Toxicoses

During the 1st induction cycle, 31 dogs had a dose reduction in 1 or more drugs. The most common dose reduction was for doxorubicin; of 71 dogs that received at least 1 doxorubicin dose, 28 dogs (39%) showed toxicity that required dose reduction or cessation of drug. Of the 28 dogs, 21 became myelosuppressed, and 7 of 21 became septic. Three of these 7 dogs died after the 2nd week of treatment due to myelosuppression and sepsis. Six dogs developed gastrointestinal signs severe enough to require hospitalization without becoming septic. One dog developed echocardiographic changes after 2 treatments.

Fifty-eight dogs received cyclophosphamide, and 13 dogs (22%) became intoxicated. Of these 13 dogs, 8 became myelosuppressed, of which 1 became septic. Nine of the 13 dogs had also had a reduction in doxorubicin dosage. Five dogs developed sterile hemorrhagic cystitis, and cyclophosphamide was replaced by chlorambucil.

Five of the 58 dogs (9%) had toxicoses attributed to L-asparaginase. Of these 5 dogs, 1 developed pancreatitis, and 4 showed pruritus, hyperaesthesia, and restlessness of sufficient severity to suspect an allergic reaction. None of these 5 dogs received further L-asparaginase.

Three dogs had reductions in the dosage of vincristine because of constipation and ileus (2 dogs) and myelosuppression (1 dog).

Of the 30 dogs that received maintenance chemotherapy or repeated induction treatments, 1 dog received no further vincristine after 9 treatments because of repeated vomiting (serum lipase was normal). One dog developed cystitis after 9 treatments of cyclophosphamide, and the drug was re-

placed with chlorambucil in the protocol. Two dogs developed pruritus, hyperactivity, and vomiting after L-asparaginase was given on the 4th and 5th treatments, respectively. One of these 2 dogs continued to receive L-asparaginase for 3 further treatments after premedication with dexamethasone and benadryl.

There were no factors identified as prognostic for an animal developing toxicoses after treatment with doxorubicin, cyclophosphamide, or L-asparaginase in combination with vincristine and prednisone, or alone.

As previously mentioned, the occurrence of toxicoses and relative dose intensity did not influence either 1st remission duration or overall protocol remission duration.

Discussion

The complete response rate in this protocol was 68%, which is identical to that seen for VELCAP-L, which used the same 12-week induction protocol.[5] As with VELCAP-L, this relatively low remission rate may reflect the evaluation of all dogs entered into this protocol, even if they received only 1 chemotherapy treatment. The inclusion of patients by ''intent to treat'' reduces the remission rate. Of the 11 dogs that received only 1 treatment, 8 were classified as substage b and presumably died or were euthanized as a result of lymphoma rather than vincristine toxicosis. The low incidence of toxicoses in other dogs after vincristine treatment alone further supports this assumption. For VELCAP-L, we proposed that a reason for the low response rate was the high number of dogs with advanced and substage b lymphoma compared with other studies; however, in this study, these percentages were 27 and 39%, respectively, which were lower than for VELCAP-L. WHO staging was applied without bone marrow cytology from all dogs, and this may be the reason that ''stage'' was not found to be an independent predictor of response. Substage was a predictor for whether or not a dog achieved remission, although the more specific categories of fever and dyspnea were the strongest independent predictors of response. Dyspnea was present in 10 dogs; only 3 of these had a mediastinal mass, and none had visible pulmonary involvement. Presumably, the respiratory signs seen in the other dogs was due to massive mandibular and pharyngeal lymphadenopathy and hence may have reflected a higher tumor burden.

Two factors, platelet count and body weight, were identified as strong predictors of remission length for dogs treated with another, similar protocol, VELCAP-L. Thrombocytopenia was an independent predictor of 1st remission duration but not overall remission duration in the VELCAP-S protocol. The reason for thrombocytopenia correlating with 1st remission duration is uncertain; however, it is possible that bone marrow involvement[12] or immune-mediated mechanisms play a role. Body weight was not correlated with achieving remission or 1st and overall remission duration in VELCAP-S. This emphasizes the problem inherent in performing multiple statistical manipulations with relatively small numbers of dogs and makes the true significance for any of these factors difficult to ascertain. Anorexia was an independent predictor of overall protocol remission duration and may be a refinement of the general finding that dogs that are unwell (substage b) have a poor prognosis.

The dose intensity of chemotherapy delivered to human patients with non-Hodgkin's lymphoma appears to influence both response rate and relapse-free survival.[13,14] In this study, we did not evaluate the influence of dose intensity on response rate, as the dogs that did not respond did not complete the induction protocol, making the contribution of dose intensity difficult to assess. We did, however, attempt to correlate dose intensity for those dogs completing the induction protocol with 1st remission duration and overall protocol remission duration. There was no marked influence seen, which may reflect the relatively low dosages used (compared to human studies), on which dosage reductions have little impact. Interestingly, 3 of the 5 dogs with long 1st remission duration had dosage reductions for doxorubicin (1 dog), cyclophosphamide (1 dog), and both drugs (1 dog).

First remission duration was relatively short, with a median duration of 20 weeks. Direct comparisons are impossible; however, it appears that the remission obtained after VELCAP-S is similar to that seen for other short-term induction chemotherapy protocols reported in the literature. The median 1st remission duration was 4 weeks from the end of a 9-week course of chemotherapy for 1 combination protocol (VCAA)[15] and 18 weeks after chemotherapy plus immunotherapy with monoclonal antibody Mab 231.[15] The median remission in a study that used short-term fractionated chemotherapy was not reported, although 4 dogs were in 1st remission at 12–44 weeks, and 3 had relapsed at 8, 30, and 32 weeks after starting chemotherapy.[7] The combination of L-asparaginase and doxorubicin for a total of 5 treatments produced a median remission duration of approximately 18 weeks.[16]

Other protocols have evaluated treatment without maintenance therapy. Doxorubicin as a single agent has resulted in median remission durations of 22 weeks[17]; however, treatment was continued up to 9 administrations (27 weeks), and animals lost to follow-up were not included in analysis. In contrast, fewer than 50% of 38 dogs treated with 3 doses of doxorubicin achieved remission for median duration of 6 weeks.[6] A recently described protocol by sequential chemotherapy for 25 weeks resulted in median remission duration of 43 weeks, when dogs that died due to toxicity were censored. Remission rate was not reported for that protocol, and nearly 30% died due to toxicity.[18]

Toxicity was common with VELCAP-S, particularly during 1st induction. Of the 71 dogs treated with the combination of doxorubicin and vincristine (week 2), 38% required a subsequent reduction in dosage. This is a high rate of toxicity compared to other reported protocols. A high-dose doxorubicin schedule (37.5 mg/m^2) resulted in 21% of dogs requiring a reduction in dosage.[18] A protocol reporting toxicity as episodes of hospitalization had a toxicity rate of 8% after single agent doxorubicin.[16] After week 2 in VELCAP-S, 18% of dogs were hospitalized. In VELCAP-S, the most common toxicity after week 2, or after cyclophosphamide, vincristine, and L-asparaginase (week 7), was myelosuppression without clinical signs. Prophylactic antibiotics were not routinely prescribed. Sepsis was less common, occurring in 7 dogs (10%) after week 2 and in 1 dog (2%)

after week 7. Sepsis, however, was the only known cause of treatment-related death and occurred in 3 dogs after treatment at week 2.

Dogs that died without achieving complete remission were commonly euthanized by their local veterinarian because of lymphoma. In dogs where details regarding the reason for euthanasia could not be obtained, it is possible that toxicity was a cause.

Of the 30 dogs that relapsed and were treated with repeated VELCAP-S induction cycles or maintenance, 26 (87%) attained a 2nd complete remission, which compares well with the 2nd remission rate of 80% seen in dogs receiving chemoimmunotherapy[19] and 74% after doxorubicin and L-asparaginase chemotherapy.[16] It has been reported that 2nd remissions are difficult to attain in dogs with lymphoma[20]; however, it appears if the relapse occurs due to cessation of treatment, rather than during continued therapy; then, reintroduction of chemotherapy is often successful. It is possible that discontinuous chemotherapy may delay the onset of drug resistance, or at least that the period of ''rest'' does not contribute to development of drug resistance; therefore, 2nd remission is more likely when relapse occurs off chemotherapy than during chemotherapy.

Overall median remission duration for dogs achieving complete remission with an identical induction protocol followed by maintenance chemotherapy (VELCAP-L) was 55 weeks, and 25% of dogs were still in remission at 110 weeks.[5] Dogs were not randomly assigned to VELCAP-L and VELCAP-S, but rather, dogs were treated with VELCAP-L before June 1994 and with VELCAP-S after June 1994. The complete remission rate was the same for both protocols. Dogs treated with VELCAP-S had a median 1st remission of 20 weeks, which was markedly different from the median remission of 55 weeks achieved with VELCAP-L ($P < .0001$). Of the VELCAP-S dogs, 5 had long, complete remissions to VELCAP-S single induction course, and 8 received 2 or 3 short courses of chemotherapy. The median overall protocol remission duration by Kaplan-Meier for this subset of 13 dogs was 88 weeks compared to 55 weeks for 68 previously reported VELCAP-L dogs. By Cox regression, the median overall protocol remission durations were not different between these 2 groups ($P = .53$). Comparison between the remission duration for the previously reported VELCAP-L dogs and the overall protocol remission duration for the entire VELCAP-S group reported here showed no statistically significant difference ($P = .28$). The median overall protocol remission duration was 44 weeks for VELCAP-S, and 36% of dogs were in remission at 52 weeks. The implication is that delaying maintenance chemotherapy until after the 2nd induction can provide the same overall remission duration as maintenance chemotherapy after the 1st induction.

In the treatment of non-Hodgkin's lymphoma in human patients, it is felt that maintenance therapy does ''no good because those who are cured do not need it, and those who are not cured may or may not be cured by [decreasing dose intensity for maintenance cycles].''[9] In this study, the same small proportion of dogs was alive in long-term remission (>18 months) and not receiving chemotherapy as was seen after the VELCAP-L protocol. Unfortunately, there did not appear to be any prognostic criteria that could identify these dogs before treatment. Of the dogs in this category, 4 were treated only with a 12-week induction cycle of chemotherapy. This tends to support the supposition that cure rate is not dependent on maintenance chemotherapy. However, although the cure rate for non-Hodgkin's lymphoma is relatively high in humans, it is low in dogs; therefore, maintenance chemotherapy may have more relevance, because it is the length of remission rather than the cure rate that determines length of survival.

The primary aim of this study was to evaluate a discontinuous dose schedule for chemotherapy for canine lymphoma. The majority of dogs received maintenance chemotherapy after their 2nd induction course of VELCAP-S because they had failed to maintain a 1st remission for longer than 16 weeks after induction chemotherapy ceased. The selection of 16 weeks was an arbitrary decision, based on a desire to allow treated dogs longer ''off'' chemotherapy than ''on'' chemotherapy. A 15-week induction as used here would require 16 weeks or more of ''off'' chemotherapy to translate into marked benefit, both financially for the owner and in quality of life for the patient. If we had selected a shorter ''off'' time period, more dogs would have received an intermittent induction protocol, but the use of multiple inductions over such a short period was not felt to be practical. The true value of discontinuous chemotherapy may be in identifying a small group of dogs that do not require maintenance chemotherapy. This advantage must be weighed against the number of dogs for which owners refuse further chemotherapy at 1st relapse. The protocol VELCAP-L caused complete remission in 68 dogs with lymphoma, and only 1 dog discontinued chemotherapy for a nonmedical reason. In the VELCAP-S protocol, 12 (21%) of the 56 dogs discontinued chemotherapy at the end of their 1st remission because of their owners' perception of poor prognosis, potential for toxicity (although dose reductions were maintained during re-induction), or inconvenience of multiple visits during re-induction. These factors should be taken into account when designing short-term protocols and will influence overall remission duration. It may be that certain owners would prefer the less intense but longer term use of maintenance chemotherapy. It is possible, then, that client compliance, as well as the option to discontinue or refuse treatment, plays a role in the effectiveness of chemotherapy for canine lymphoma.

References

1. Ogilvie GK, Moore AS. Management of specific diseases: Lymphoma. In: Managing the Veterinary Cancer Patient. Trenton, NJ: Veterinary Learning Systems; 1995:228–259.

2. Stone MS, Goldstein MA, Cotter SM. Comparison of two protocols for the induction of remission in dogs with lymphoma. J Am Anim Hosp Assoc 1991;27:315–321.

3. Myers NC, Moore AS, Cotter SM, et al. Evaluation of a multidrug chemotherapy protocol (ACOPA-II) for the treatment of dogs with lymphoma. J Vet Intern Med 1998;11:333–339.

4. Keller ET, MacEwen EG, Rosenthal RC, et al. Evaluation of prognostic factors and sequential combination chemotherapy for canine lymphoma. J Vet Intern Med 1993;7:289–295.

5. Zemann BI, Moore AS, Rand WM, et al. A combination chemotherapy protocol (VELCAP-L) for the treatment of canine lymphoma. J Vet Intern Med 1998;12:465–470.

6. Hahn K, Richardson R, Teclaw R, et al. Is maintenance che-

motherapy appropriate for the management of canine lymphoma? J Vet Intern Med 1992;6:3–10.

7. Rosenthal RC. Short-term fractionated combination chemotherapy for the treatment of lymphoma in dogs. Proceedings of the 13th Annual Conference of the Veterinary Cancer Society, 1993.

8. Kaufman D, Chabner BA. Clinical strategies for canine lymphoma treatment: The role of drugs. In: Chabner BA, Long DL, eds. Cancer Chemotherapy and Biotherapy, Principles and Practice, 2nd ed. Philadelphia, PA: Lippincott-Raven; 1996:1–16.

9. DeVita VT, Jr. Is alternating cyclic chemotherapy better than standard four-drug chemotherapy for Hodgkin's disease? No. Principles Pract Oncol Updates 1993;7:1–11.

10. DeVita VT, Jr. Principles of chemotherapy. In: DeVita VT, Jr, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology, 3rd ed. Philadelphia, PA: JB Lippincott; 1989:276–300.

11. Owen L. TNM classification of tumors in domestic animals. Geneva: WHO; 1980:46–47.

12. Madewell BR. Hematological and bone marrow cytological abnormalities in 75 dogs with malignant lymphoma. J Am Anim Hosp Assoc 1986;22:235–240.

13. Dodwell DJ, de Campos ES, Radford JA. Chemotherapy for Hodgkin's disease and aggressive non-Hodgkin's lymphoma; more is better, or is it? Drugs 1992;44:1–8.

14. Linch DC. Dose optimisation and dose intensification in malignant lymphoma. Eur J Cancer 1994;30A:122–125.

15. Jeglum KA. Monoclonal antibody treatment of canine lymphoma. Proc Eastern States Vet Conf 1991;5:222–223.

16. Valerius KA, Ogilvie GK, Mallinckrodt CH, Getzt DM. Doxorubicin alone or in combination with asparaginase, followed by cyclophosphamide, vincristine, and prednisone for treatment of multicentric lymphoma in dogs: 121 cases (1987–1995). J Am Vet Med Assoc 1997;210:512–516.

17. Postorino NC, Susaneck SJ, Withrow SJ, et al. Single agent therapy with Adriamycin for canine lymphosarcoma. J Am Anim Hosp Assoc 1989;25:221–225.

18. Chun R, Garrett LD, Vail DM. Evaluation of a high-dose chemotherapy protocol with no maintenance chemotherapy for dogs with lymphoma. J Vet Intern Med 2000;14:120–124.

19. Jeglum KA. Chemoimmunotherapy of canine lymphoma with adjuvant canine monoclonal antibody 231. Vet Clin North Am 1996; 26:73–85.

20. MacEwen EG, Young KM. Canine lymphoma and lymphoid leukemias. In: Withrow SJ, MacEwen EG, eds. Small Animal Clinical Oncology, 2nd ed. Philadelphia, PA: WB Saunders; 1996:451–479.