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Efficacy of Combination Chemotherapy for Treatment of Gastrointestinal Lymphoma in Dogs

K.M. Rassnick, A.S. Moore, K.E. Collister, N.C. Northrup, O. Kristal, J.D. Chretin, and D.B. Bailey

Background: Chemotherapy for multicentric canine lymphoma has favorable results. The gastrointestinal (GI) tract is the most common extranodal site of canine lymphoma, but there have been no prospective studies to determine outcome when dogs with GI lymphoma are treated with chemotherapy.

Hypothesis: Treatment with a multiagent chemotherapy protocol is associated with a poor outcome in dogs with GI lymphoma.

Animals: Eighteen dogs with histologically confirmed GI lymphoma.

Methods: Prospective clinical trial in which dogs with GI lymphoma were treated with a 20-week combination chemotherapy protocol consisting of induction and consolidation phases.

Results: Thirteen dogs had primary GI lymphoma and 5 had multicentric lymphoma with GI involvement. The majority of the lymphomas (63%) were of T-cell origin. Overall remission rate was 56%; 9 dogs achieved a complete remission for a median of 86 days (range, 22–420 days) and 1 dog achieved a partial remission for 26 days. Overall median survival time was 77 days (range, 6–700 days). Dogs that failed to achieve a remission (10 versus 117 days; $P = .002$) or had diarrhea at initial presentation (70 versus 700 days; $P < .001$) had shorter survival times.

Conclusion and Clinical Importance: The response and survival of dogs with GI lymphoma treated with multiagent chemotherapy is poor but long-term survival is possible.

Key words: Canine; Gastroenterology; Oncology treatment.

Gastrointestinal (GI) lymphoma is uncommon in dogs, but the GI tract represents the most frequently involved extranodal site, accounting for approximately 7% of all canine lymphomas and 5–7% of canine GI neoplasms.[1,2] GI lymphoma is an extension of multicentric lymphoma in some dogs, but the majority of cases the GI tract appears to be the primary location with no clinical evidence of disease extending outside of the abdominal cavity.[3,4] Compared with the amount of information available in the literature regarding the treatment of canine multicentric lymphoma, information on treating canine GI lymphoma is limited. Most publications are retrospective reviews[4,5] or case reports.[6–10] Others do not distinguish between anatomic sites, including cases of GI lymphoma in the evaluation of treatment outcome in large populations of dogs with lymphoma.[11–14] The present clinical trial represents the 1st prospective study evaluating the response of canine GI lymphoma to a uniform, multiagent chemotherapy protocol: VELCAP-SC (vincristine,[a] L-asparaginase,[b] cyclophosphamide,[c] doxorubicin,[d] and prednisone[e]—short, consolidated; Table 1).

The VELCAP-SC protocol was originally developed to treat dogs with advanced stage and substage b lymphoma that did not qualify for competing funded studies.[15] The denotation ''short'' refers to the discontinuous design of the protocol; VELCAP-SC is a short-term (20-week) protocol that does not include a maintenance phase. The ''consolidation'' portion of the protocol is the introduction of new drugs (lomustine [CCNU[f]] and MOPP [mechlorethamine,[g] vincristine, procarbazine,[h] and prednisone]) after dogs have achieved complete remission (CR) in the initial 11-week induction phase of the VELCAP-SC protocol. Ten dogs with GI lymphoma were included in the original group[15] treated with VELCAP-SC and GI anatomic location was a factor significantly associated with shorter survival time; median survival time of 10 dogs with GI lymphoma was 77 days compared with 302 days for 94 dogs with multicentric lymphoma ($P = .019$). To better characterize their response to chemotherapy, we elected to omit the 10 cases with GI lymphoma from the manuscript[15] and continue prospective treatment of additional dogs with confirmed GI involvement.

The purpose of the present study was to evaluate the clinical characteristics and outcome of dogs with GI lymphoma treated with the VELCAP-SC protocol. An additional objective was to evaluate the importance of factors that might influence the response to treatment or survival.

Materials and Methods

Study Subjects

For inclusion into this trial, dogs were required to have histologically proven high-grade lymphoma involving the GI tract (excluding the oral cavity and esophagus). Dogs with concurrent extra-GI involvement were eligible.

From the Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY (Rassnick, Bailey); and the Harrington Oncology Program, Cummings School of Veterinary Medicine at Tufts University, North Grafton, MA (Rassnick, Moore, Collister, Northrup, Kristal, Chretin). Dr Moore is presently affiliated with Veterinary Oncology Consultants, Wauchope, Australia. Dr Collister is presently affiliated in Glenview, IL. Dr Northrup is presently affiliated with College of Veterinary Medicine, University of Georgia, Athens, GA. Dr Kristal is presently affiliated with Chavat Daat Veterinary Specialty Center, Bet Berl, Kfar Saba, Israel. Dr Chretin is presently affiliated with Veterinary Centers of America, West Los Angeles Animal Hospital, Los Angeles, CA. Dr Bailey is presently affiliated with Oradell Animal Hospital, Paramus, NJ.

Corresponding author: Kenneth Rassnick, DVM, DACVIM, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, PO Box 31, Ithaca, NY 14853; e-mail: kmr32@cornell.edu.

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Table 1. VELCAP-SC chemotherapy protocol used for the treatment of 18 dogs with gastrointestinal lymphoma.

Week	Drug	Dosage and Route
1	L-Asparaginase	10,000 U/m^2 SQ
	Vincristine	0.75 mg/m^2 IV
	Prednisone	40 mg/m^2 PO × 7 day
2	Vincristine	0.75 mg/m^2 IV
	Prednisone	40 mg/m^2 PO q48h × 7 day
3	Doxorubicin	1 mg/kg IV (if <1 m^2) 30 mg/m^2 IV (if ≥ 1 m^2)
	Prednisone	20 mg/m^2 PO q48h × 7 day
4	L-Asparaginase	10,000 U/m^2 SQ
	Prednisone	20 mg/m^2 PO q48h × 7 day
5	Vincristine	0.75 mg/m^2 IV
	Cyclophosphamide[a]	250 mg/m^2 PO
	Prednisone	10 mg/m^2 PO q48h × 7 day
7	Doxorubicin	1 mg/kg IV (if <1 m^2) 30 mg/m^2 IV (if ≥ 1 m^2)
9	Vincristine	0.75 mg/m^2 IV
	Cyclophosphamide[a]	250 mg/m^2 PO
11	Doxorubicin	1 mg/kg IV (if <1 m^2) 30 mg/m^2 IV (if ≥ 1 m^2)
13	Mechlorethamine	3 mg/m^2 IV
	Vincristine	0.75 mg/m^2 IV
	Procarbazine	50 mg/m^2 PO × 14 day
	Prednisone	40 mg/m^2 PO × 14 day
14	Mechlorethamine	3 mg/m^2 IV
	Vincristine	0.75 mg/m^2 IV
17	CCNU	90 mg/m^2 PO
20	CCNU	90 mg/m^2 PO

Weeks 1–11 are the induction phase and weeks 12–20 are the consolidation phase.

[a]Furosemide (2 mg/kg PO) was given concurrently with cyclophosphamide.

Diagnosis and Staging

The diagnosis of lymphoma was made on examination of biopsy specimens from at least 1 GI lesion. Immunophenotype was established on paraffin-embedded sections by use of antibodies against BLA36,[i] CD79a,[j] and CD3.[k] The initial staging diagnostic evaluation performed in all dogs included a physical examination, CBC with cytologic smear evaluated by a clinical pathologist, serum biochemical profile, urinalysis, thoracic radiography, abdominal ultrasonography, and bone marrow aspiration cytology. Based on World Health Organization (WHO) criteria for canine lymphoma, all dogs were stage V because of their GI involvement.[16] Dogs were further classified as either substage a (having no clinical signs) or substage b (having clinical signs including GI [vomiting, diarrhea, inappetence] or respiratory signs, hypercalcemia [>12 mg/dL], fever [>103°F], hyphema, or uveitis). Dogs with lymphoma limited to the GI tract with or without concurrent extra-GI involvement confined to the abdominal cavity or bone marrow were classified as having primary GI lymphoma. Dogs with GI lymphoma and involvement of thoracic or peripheral lymph nodes were classified as having GI lymphoma as a manifestation of multicentric lymphoma.

VELCAP-SC Treatment Protocol

Dogs with GI lymphoma were treated with the VELCAP-SC protocol (Table 1). A CBC was performed before each treatment. Scheduled treatments were delayed 2–5 days if the pretreatment neutrophil count was $<1{,}500$ cells/μL or if GI toxicity $\geq$grade 2[17] was observed upon presentation for treatment. If administration of a chemotherapy drug resulted in neutropenia or GI toxicity $\geq$grade 3,[17] subsequent treatments with that drug were administered at a 25%-decreased dosage. After treatment with CCNU, dogs received prophylactic antibiotics (trimethoprim-sulfadiazine,[l] 15 mg/kg PO q12h). If administration of CCNU on week 17 resulted in neutropenia $\geq$grade 4, the subsequent week 20 dosage was decreased to 70 mg/m^2.

Assessment of Response

Dogs underwent a complete physical examination before each treatment. Abdominal ultrasonography was repeated on weeks 4, 9, 13, and 17 of the VELCAP-SC protocol (Table 1). Additional examinations were done during the protocol based on results of physical examination or review of the medical history. CR was defined as the resolution of all clinical signs and disappearance of all clinical evidence of disease based on physical examination, radiography, and ultrasonography. Partial remission (PR) was defined as $\geq$50% but $<$100% reduction in size of all measurable disease. For this study, all CRs and PRs had to be sustained for at least 21 days. No response was defined as CR or PR persisting for $<$21 days, $<$50% reduction in the size of measurable disease, increase in size of measurable disease during the initial 3 weeks, or appearance of new lesions during the initial 3 weeks. Dogs that died, regardless of cause, or were lost to follow-up before 21 days, were considered to have not responded. After completion of the VELCAP-SC protocol, dogs were rechecked on a monthly basis to evaluate remission status; a full medical history, physical examination, and abdominal ultrasound examination were done at each recheck. Relapse was defined as recurrence of organ or lymph node enlargement after CR or progression of disease ($\geq$25% increase in size) for dogs with a PR.

Dogs that relapsed after completing the treatment protocol were reinduced with VELCAP-SC followed by continuous maintenance therapy. Maintenance therapy consisted of a combination of vincristine (0.75 mg/m^2 IV) and cyclophosphamide (250 mg/m^2 PO) every 3 weeks for 2 treatments followed by vincristine (0.75 mg/m^2 IV) and actinomycin-D[m] (0.5 mg/m^2 IV) 3 weeks later. Dogs receiving cyclophosphamide were treated concurrently with furosemide[n] (2 mg/kg PO). This 9-week cycle was repeated for 18 months or until relapse. If dogs relapsed a 2nd time, they were started on appropriate rescue chemotherapy protocol(s).

Assessment of Toxicity

A CBC was performed weekly after each chemotherapy session. Information about GI toxicosis was obtained from client questionnaires. Treatment-associated hematological and GI toxicoses were graded from 1 to 5 according to the Veterinary Co-Operative Oncology Group Common Terminology Criteria for Adverse Events (version 1).[17]

Statistical Analysis

All dogs that began treatment with the VELCAP-SC protocol were included in analyses of response rate and duration and survival time. Overall response rate was defined as the number of dogs with CR or PR divided by the number of dogs treated. CR and PR rates were defined as numbers of dogs with CR or PR divided by the number of dogs treated. First remission duration was defined as the time in days from which a dog first achieved CR or PR until relapse. Overall remission duration included the 1st remission duration plus any subsequent remission achieved by the resumed VELCAP-SC and maintenance chemotherapy protocols. Dogs were censored in remission duration analysis for the following reasons: relapse had not occurred before the end of the study, lost to follow-up, or died before relapse. Survival time was defined as the time

from 1st day of chemotherapy until death from any cause. Dogs were censored in survival analysis if alive at the end of the study or lost to follow-up.

Risk factors analyzed to determine their effect on response to treatment and survival included age, weight, sex, immunophenotype (B-cell versus T-cell), number of GI lesions (single versus multiple or diffuse), GI lymphoma classification (primary GI lymphoma versus GI lymphoma as a manifestation of multicentric lymphoma) and the following yes/no variables: vomiting, diarrhea, lethargy, fever, inappetence, any GI clinical signs, corticosteroid pretreatment (for $\geq$7 days), resection-anastomosis performed, hypoalbuminemia ($<$3.0 mg/dL), and decrease in chemotherapy dosage because of toxicity. Normal distribution of values was evaluated by drawing a histogram. The Student's *t*-test (for the 2 continuous variables) and χ^2 test of independence and Fisher's exact test (for the categorical and yes/no variables) were used to screen data for association with response to therapy (CR or PR versus no response). The Kaplan-Meier product limit method was used to estimate response duration and survival curves for each potential risk factor listed above as well as type of remission (CR and PR versus no response). For each categorical risk factor, the log rank test for censored data was used to compare curves. The Pearson correlation test was used to assess the association between remission duration or survival time and any continuous variable. To evaluate the combined effects of potential risk factors on response duration and survival, multivariable survival analysis was done using forward conditional Cox regression analysis. The Bonferroni correction was used to correct for multiple testing. Variables with P values $\leq$ .006 in the univariable analysis were subjected to multivariable analysis. All statistical analyses were performed by use of a software package.[o] For final analysis, values of $P < .003$ (2 sided) were considered significant.

Results

Study Subject Characteristics

Eighteen dogs with GI lymphoma were treated with VELCAP-SC between April 1997 and August 2006. Ten were males (6 castrated) and 8 were females (all spayed). Purebred dogs represented by 10 different breeds accounted for 72% (13 of 18) of the dogs. Breeds with more than 1 affected dog included Golden Retrievers (n = 3) and Rottweilers (n = 2). Breeds with 1 affected dog each included Airedale Terrier, Bernese Mountain Dog, Boxer, Miniature Schnauzer, Siberian Husky, Labrador Retriever, Old English Sheepdog, and Shar-Pei. The remaining 28% (5 of 18) were mixed breed dogs. The median body weight was 27 kg (range, 9–54 kg) and the median age was 10 years (range, 3–15 years). Eleven (61%) dogs had previously been treated with corticosteroids; 7 (39%) had not received any previous treatment.

All dogs were substage b. Common clinical signs at the time of hospital administration included vomiting (13 of 18, 72%), diarrhea (13 of 18, 72%), inappetence (12 of 18, 67%), and lethargy (12 of 18; 67%). Two dogs had fever (temperature $>$103°F). Dogs frequently had $>$1 clinical sign at the time of hospital admission.

Hypoalbuminemia was a common abnormal clinicopathologic finding. Sixty-one percent (11 of 18) of the dogs had low serum albumin concentrations (range, 1.6–2.9 g/dL; reference range, 3.1–4.1 g/dL). One dog had increased serum bilirubin (5.8 mg/dL; reference range, 0.04–0.4 mg/dL). All dogs were normocalcemic and none had evidence of bone marrow involvement based on cytologic evaluation of bone marrow aspirates.

The histologic diagnosis of lymphoma was made from GI tissues obtained by exploratory laparotomy with resection and anastomosis of a mass in 8 dogs or full-thickness intestinal biopsies in 2 dogs, ultrasound-guided percutaneous Tru-cut biopsy in 7 dogs, and gastroduodenal endoscopy in 1 dog. All 8 dogs that underwent resection and anastomosis of a mass still had gross disease in the liver or spleen (n = 4), abdominal lymph nodes (n = 3), or peripheral lymph nodes (n = 1). Eleven dogs had a single GI lesion, 4 had multiple GI lesions, and 3 had diffuse GI involvement. Thirteen (72%) dogs had primary GI lymphoma and 5 (28%) dogs had multicentric lymphoma with GI involvement. Immunophenotyping analysis was available from 16 biopsy specimens. There were 10 (63%) T-cell and 6 (37%) B-cell lymphomas (Table 2).

Table 2. Frequencies of sites affected in 18 dogs with gastrointestinal lymphoma.

Anatomic Classification	Sites Affected	Total No. of Cases	No. of GI Lesions[a]	Immunophenotype[b]	
				T-Cell	B-Cell
Primary GI	SI, mesenteric LN	5	1 (n = 4), diffuse (n = 1)	3	1
	SI, liver	2	1 (n = 2)	1	0
	SI only	1	Diffuse	0	1
	SI, spleen	1	2	1	0
	SI, liver, spleen	1	3	1	0
	SI, liver, spleen, mesenteric LN	1	1	0	1
	SI, LI, mesenteric LN	1	4	0	1
	Colon, medial iliac LN	1	1	1	0
GI with multicentric disease	Stomach, hepatic LN, peripheral LN	1	1	0	1
	SI, mesenteric LN, cutaneous nodules	1	Diffuse	1	0
	SI, spleen, thoracic LN, peripheral LN	1	1	1	0
	SI, spleen, peripheral LN	1	3	0	1
	SI, peripheral LN	1	1	1	0

[a]Based on exploratory laparotomy (n = 10) or abdominal ultrasonography (n = 8).
[b]Not all dogs had immunophenotyping performed.
GI, gastrointestinal; SI, small intestines; LN, lymph nodes; LI, large intestine.

Response to Treatment

All 18 dogs with GI lymphoma had gross disease when the VELCAP-SC protocol was started and response to treatment was evaluated in all cases. Eight dogs were nonresponders and were euthanized because of progressive lymphoma 6–77 days after starting treatment. Ten dogs responded for an overall response rate of 56% (95% CI, 34–75%). Nine (50%) dogs achieved CR and 1 (6%) achieved PR. Of the 13 dogs with primary GI lymphoma, 7 achieved CR and the remaining 6 dogs were nonresponders. Of the 5 dogs with GI lymphoma as a manifestation of multicentric lymphoma, 2 achieved CR and 1 achieved PR; the remaining 2 dogs failed to respond. Phenotype was available for 8 of the 10 dogs that responded to VELCAP-SC; 3 had T-cell lymphoma (all achieved CR) and 5 had B-cell lymphoma (4 achieved CR, 1 achieved PR). The 2 dogs with missing immunophenotype information both achieved CR. No significant difference was found between responders (CR or PR) and nonresponders with respect to any of the analyzed risk factors.

Remission Duration

Of the 10 responders, 8 relapsed or progressed and 2 dogs in CR were censored at the time of data analysis (1 died as a result of chemotherapy toxicity 22 days after treatment and 1 was lost to follow-up 46 days after treatment). The median 1st remission duration was 86 days (95% CI, 70–102 days) and the estimated probability that dogs still would be in their 1st remission 6 months after achieving remission was 25%. Three dogs completed the VELCAP-SC protocol in CR and relapsed 182–218 days after starting therapy. Two of these dogs achieved a 2nd CR when reinduced with VELCAP-SC. The 3rd dog was treated only with corticosteroids upon relapse. The median overall remission duration was 86 days (95% CI, 70–102 days; Fig 1) and the estimated probability that dogs would be in remission 6 months after achieving remission was 38%. Median remission duration for the 9 dogs that achieved a CR was 86 days; 1 dog sustained a PR for 26 days. None of the other dogs that relapsed after an initial response to VELCAP-SC and none of the dogs that failed to respond initially to VELCAP-SC were treated with rescue chemotherapy regimens. None of the evaluated risk factors was significantly associated with remission duration for all dogs with GI lymphoma.

Overall Survival

Sixteen dogs died during the follow-up period; 15 died from progressive GI lymphoma and 1 from chemotherapy-associated toxicity. One dog with a resected small intestinal mass and positive mesenteric lymph node (unknown immunophenotype) relapsed on day 182 but was treated with corticosteroids and remained alive at the time of data accrual (420 days after starting chemotherapy). One dog in CR was lost to follow-up on day 46. The overall survival curve analysis indicated that the median survival time was 77 days (95% CI, 34–120 days; Fig 2) and the estimated probabilities of survival 6 and 12 months after starting chemotherapy were 25 and 18%, respectively. Median overall survival times for 13 dogs with primary GI lymphoma and 5 dogs with GI lymphoma as a manifestation of multicentric disease were 77 days (95% CI, 35–119 days) and 106 days (95% CI, 0–319 days), respectively ($P = .76$). Median survival time for 6 dogs with B-cell GI lymphoma was 106 days (95% CI, 0–359 days) and the median survival time for 10 dogs with T-cell GI lymphoma was 22 days (95% CI, 0–103 days; $P = .06$). In multivariate analysis, risk factors significantly associated with shorter survival times were type of remission ($P = .002$), and diarrhea ($P < .001$). The median survival time of 8 nonresponders was 10 days (95% CI, 7–13 days) and the median survival time of 10 dogs that responded (CR or PR) was 117 days (95% CI, 85–149 days). The median survival time of 13 dogs with diarrhea as an initial clinical sign was 70 days (95% CI, 6–135 days)

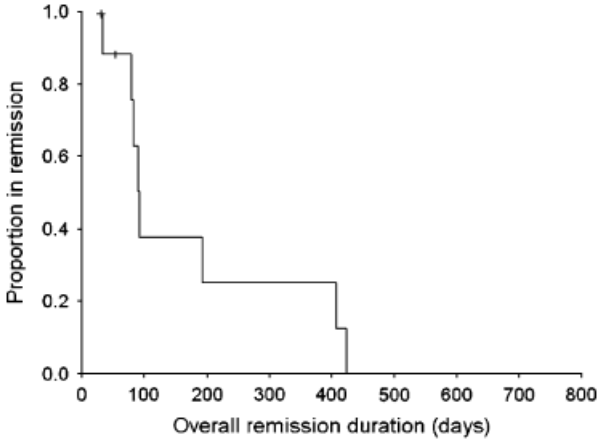

Fig 1. Kaplan-Meier curve depicting remission duration in 10 of 18 dogs with gastrointestinal lymphoma that achieved a complete (n = 9) or partial (n = 1) remission to treatment with the VELCAP-SC chemotherapy protocol. The median overall remission duration was 86 days (95% CI, 70–102 days). Vertical marks represent censored data.

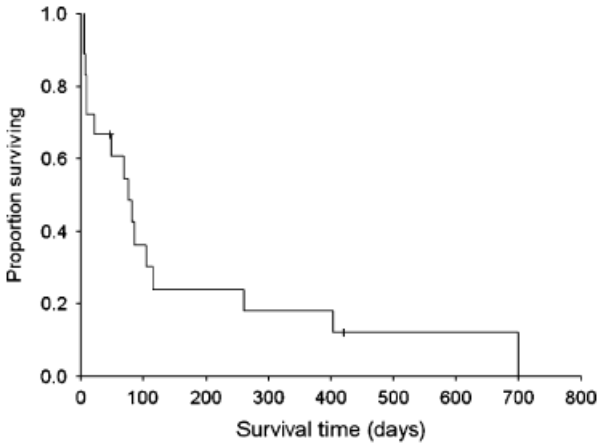

Fig 2. Kaplan-Meier curve depicting survival time of 18 dogs with gastrointestinal lymphoma treated with the VELCAP-SC protocol. The overall median survival time was 77 days (95% CI, 34–120 days). Vertical marks represent censored data.

compared with 700 days (95% CI, lower and upper limits undefined) for 5 dogs without diarrhea.

Toxicosis

Six dogs (4 in CR and 2 nonresponders) with GI lymphoma treated with VELCAP-SC experienced ≥grade 3 GI toxicosis after vincristine and required subsequent decreases in dosage. One of the 6 dogs also had an adverse GI episode after doxorubicin and an adverse GI episode after cyclophosphamide, both necessitating decreases in dosages. Importantly, because of failure to respond to therapy and progression of disease, all dogs in this study did not necessarily receive all intended drugs of the VELCAP-SC protocol.

Discussion

The goals of this study were to describe the outcome of dogs with GI lymphoma (all treated with a uniform multiagent chemotherapy protocol) and identify factors that might be prognostic for response or survival. Of the 18 dogs with GI lymphoma in this study, only 10 dogs achieved CR and the overall median survival was short; the median survival with chemotherapy was 2.5 months, with only 18% of dogs surviving longer than 12 months. Of the factors analyzed, diarrhea as an initial clinical sign was associated with short survival time. For 5 dogs with diarrhea, the median survival time was 2.5 months, compared with 30 months for 13 dogs without diarrhea. Although speculative, diarrhea may be a surrogate marker for anatomic location, severity of disease or both. Additionally, diarrhea might contribute to perception of poor quality of life by the owner. Lack of response to chemotherapy was also associated with shorter survival time. The median survival time of 8 dogs that failed to respond to chemotherapy was 10 days, compared with 3.8 months for 10 dogs that achieved CR or PR. This result seems logical, but similar results have not always been observed in cats with GI lymphoma.[18,19] No other prognostic factors were identified, but evaluation of a larger sample size may have permitted discovery of additional characteristics of dogs with GI lymphoma that are associated with response to therapy or survival.

This is the 1st study in which dogs with GI lymphoma were prospectively evaluated while being treated with a VELCAP-type protocol. VELCAP-SC is a short-term (pulse) chemotherapy protocol with a consolidation phase consisting of alkylating agents.[15] This protocol was chosen to treat dogs with GI lymphoma to evaluate their response to a uniform, multiagent chemotherapy protocol, not to test the necessity of a maintenance phase or the benefit of a consolidation phase. In fact, as a consequence of dogs not achieving a remission and a poor overall median survival time, less than half of the dogs lived to receive the consolidation portion of the protocol.

Canine GI lymphoma is most commonly of T-cell origin. Of 80 dogs in 4 reports, 62 (78%) had T-cell, 10 (12%) had B-cell, and 8 (10%) had null-cell lymphoma.[3,5,8,20] The T-cell phenotype in canine high-grade lymphoma generally is associated with a poor response to chemotherapy.[14,21] In the current study, median survival of dogs with T-cell GI lymphoma was 3 weeks compared with 3 months for dogs with B-cell GI lymphoma. This difference did not reach statistical significance ($P = .06$). Some authors have suggested outcomes of dogs with multicentric high-grade T-cell lymphoma might be improved when alkylating agents are included early in the treatment regimen.[15] Although VELCAP-SC includes a consolidation phase of alkylating agents, less than half of the dogs received that portion of the protocol. It may be possible to improve the overall prognosis for dogs with GI lymphoma, especially T-cell GI lymphoma, by including alkylating agents as part of initial therapy but more information about immunophenotype and response to combination chemotherapy is needed.

Dogs with GI lymphoma generally have a worse response to therapy than do dogs with lymphoma primarily affecting peripheral lymph nodes or other extranodal sites. This perception has led some authors to classify dogs with GI lymphoma into a modified WHO stage category (stage VI).[5,11] The conclusion that canine GI lymphoma has a different biological behavior has been reached by comparing dogs treated with different protocols or comparing different populations based on medians rather than direct statistical comparison. The initial reason for performing this study was our preliminary statistical finding that dogs treated for GI lymphoma with VELCAP-SC had a worse prognosis for survival. All dogs with lymphoma treated with VELCAP-SC were subjected to posthoc analysis to evaluate variables affecting survival. This included the 18 dogs with GI lymphoma reported here and 94 dogs with multicentric lymphoma treated between 1997 and 2000 (reported by Morrison-Collister et al[15]). GI location was significantly associated with shorter survival time on univariate analysis; dogs with GI lymphoma had a median survival of 77 days and dogs with multicentric lymphoma without GI involvement had a median survival of 302 days ($P = .003$). However, GI location did not remain significant upon multivariate analysis ($P = .064$). Future studies with larger numbers of patients to confirm this finding are warranted. Furthermore, all dogs with GI lymphoma had GI signs, abdominal ultrasonography, and histopathology that ultimately led to confirmation of their disease. Abdominal ultrasonography was a routine staging test for dogs with lymphoma in the original VELCAP-SC study.[15] Nevertheless, it is possible that GI lesions were missed in that group of dogs thereby including cases with lymphoma affecting the GI tract. This erroneous classification is a form of "stage migration" and raises the possibility that results comparing 2 groups that are thought to be affected and not affected may be inaccurate.[22]

Footnotes

[a] Vincristine, Mayne Pharma Inc, Paramus, NJ
[b] Elspar, Merck & Co Inc, Whitehouse Station, NJ
[c] Cytoxan, Roxanne Laboratories Inc, Columbus, OH
[d] Adriamycin, Bedford Laboratories, Bedford, OH
[e] Prednisone, Roxanne Laboratories Inc
[f] CeeNu, Bristol Laboratories, Princeton, NJ

[g] Mustargen, Ovation Pharmaceuticals, Deerfield, IL
[h] Matulane, Sigma-Tau, Gaithersburg, MD
[i] BLA36, Dako, Carpinteria, CA
[j] CD79a, Dako
[k] CD3, Zymed, South San Francisco, CA
[l] Tribrissen, Interfarm, Hauppauge, NY
[m] Cosmegen, Ovation Pharmaceuticals
[n] Salix, Pathoen YM Inc, Toronto, ON, Canada
[o] SPSS 10, Statistical Analytical Software, Chicago, IL

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