Outcome of cats with low-grade lymphocytic lymphoma: 41 cases (1995–2005)

Michael A. Kiselow, DVM; Kenneth M. Rassnick, DVM, DACVIM; Sean P. McDonough, DVM, PhD, DACVP; Richard E. Goldstein, DVM, DACVIM; Kenneth W. Simpson, BVMS, PhD, DACVIM; Tristan K. Weinkle, DVM, DACVIM; Hollis N. Erb, DVM, PhD

Objective—To evaluate factors associated with response to treatment, remission duration, and survival in cats with low-grade lymphoma affecting various organ systems.

Design—Retrospective case series.

Sample Population—41 cats with histologically confirmed low-grade lymphocytic lymphoma.

Procedures—Medical records and biopsy specimens of cats with histologically confirmed low-grade lymphocytic lymphoma of various organ systems treated with prednisone and chlorambucil between 1995 and 2005 were reviewed. The Kaplan-Meier method was used to estimate remission duration and survival. Factors potentially associated with prognosis were compared.

Results—Common clinical signs were weight loss (83%), vomiting (73%), anorexia (66%), and diarrhea (58%). Seventy-eight percent of cats tested had low serum cobalamin concentrations. Lymphoma was confined to the gastrointestinal tract in 68% of cats. Fifty-six percent of cats achieved a complete response to treatment, and 39% achieved a partial response. Five percent of cats had no response. No association was found between any risk factors (including anatomic site) and response to treatment. Partial response was associated with shorter remission duration, compared with complete response; median remission duration was 428 days for cats achieving a partial response, compared with 897 days for cats achieving a complete response. No other factors were associated with remission duration. Overall median survival time was 704 days. No factors were significantly associated with survival time.

Conclusions and Clinical Relevance—Most cats with lymphocytic lymphoma responded to treatment with prednisone and chlorambucil, and most factors evaluated were not associated with outcome. (*J Am Vet Med Assoc* 2008;232:405–410)

Lymphoma in cats represents a diverse group of lesions that vary in cell type, rate of dissemination, and progression. The National Cancer Institute Working Formulation has been used to histologically classify lymphomas of cats into low-, intermediate-, and high-grade categories.[1] Most lymphomas in cats are intermediate (35%) or high (54%) grade[1] and behave similarly to rapidly progressive diseases that are almost uniformly fatal despite aggressive chemotherapy. Approximately 10% of lymphomas of cats are composed of small, relatively well-differentiated, neoplastic lymphoid cells and can be histologically described as low grade.[1-4] The National Cancer Institute Working Formulation was created from a need to devise classification schemes for lymphoma in humans on the basis of histologic subtype that also convey relevant information regarding expected biologic behavior. These histologic criteria have been evaluated for lymphomas of cats and were found to be applicable.[1] Many clinical reports have been published describing the diagnosis, treatment, and prognosis in cats with lymphoma. However, although the occurrence of low-grade lymphomas among study populations is sporadically documented, all cats typically undergo identical treatment protocols, without distinction between histologic grade and clinical outcome.[2-6]

Abbreviations

CL	Confidence limit
CI	Confidence interval

To date, only a single study[7] specifically followed a group of cats afflicted with low-grade lymphoma; only cats with disease confined to the intestinal tract were evaluated. Eleven cats with high-grade lymphoma of the gastrointestinal tract were treated with multidrug combination chemotherapy protocols and were compared with 29 cats with low-grade lymphocytic lymphoma of the gastrointestinal tract that were treated with prednisone and chlorambucil; the latter population had a significantly greater response to treatment, disease-free interval, and overall survival.[7] Although that study[7] was the first to define and treat low-grade lymphoma

From the Departments of Clinical Sciences (Kiselow, Rassnick, Goldstein, Simpson), Biomedical Sciences (McDonough), and Population Medicine and Diagnostic Sciences (Erb), College of Veterinary Medicine, Cornell University, Ithaca, NY 14853; and South Carolina Veterinary Internal Medicine, 132 Stonemark Ln, Columbia, SC 29210 (Weinkle).

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Address correspondence to Dr. Rassnick.

as a discrete clinical entity, limitations included a fairly small number of treated cats, restriction of disease solely to the gastrointestinal tract, and the use of endoscopy to collect most biopsy specimens, which precluded histologic evaluation of full-thickness tissue sections.

The purpose of the study reported here was to compare the clinical outcome of cats with low-grade lymphocytic lymphoma of the gastrointestinal tract with outcome for cats with low-grade lymphocytic lymphoma affecting other organ systems. A secondary objective of the present study was to describe clinical signs at the time of hospital admission and evaluate the importance of other factors that might be associated with response to treatment and survival.

Materials and Methods

Case selection—Medical records of cats with a diagnosis of lymphoma at the Cornell University Hospital for Animals, College of Veterinary Medicine, Cornell University and South Carolina Veterinary Internal Medicine, Columbia, SC, from 1995 to 2005 were retrospectively reviewed. Only cats with histopathologically confirmed low-grade lymphocytic lymphoma treated with a combination of prednisone[a] and chlorambucil[b] were included in the study. Affected cats with low-grade lymphoma with missing histologic slides of sections of biopsy specimens or inadequate follow-up information were excluded.

Medical records review—Information recorded from medical records included signalment, clinical signs at the time of hospital admission, duration of signs, treatments prior to confirmed diagnosis, results of diagnostic tests, method of biopsy specimen collection, anatomic sites affected, immunophenotype, response to treatment with prednisone and chlorambucil, and date of death. Results of postmortem examinations were recorded when available.

For purposes of the study, disease was considered to be located in the gastrointestinal tract if histologic findings revealed low-grade lymphocytic lymphoma of the stomach, small intestine, or large intestine. The disease was considered nongastrointestinal when histologic findings revealed low-grade lymphoma of any other organ system, with or without gastrointestinal tract involvement.

Histologic evaluation—Histologic slides of sections of biopsy specimens of all cats were reviewed by 1 pathologist (SPM) to confirm the diagnosis. Cats were classified as having low-grade lymphocytic lymphoma on the basis of published criteria.[8,9] Immunophenotyping was performed on the archived tissues by use of antibodies to CD79a,[c] BLA.36,[c] and CD3[c]; immunohistochemical staining was done as per the instructions of the manufacturer[c] and previously described methods.[10]

Treatment response—Duration of disease was defined as the interval between the onset of clinical signs, as reported in the medical record, and histopathologic diagnosis of low-grade lymphoma. Response to treatment was assessed by the examining clinician and was categorized as complete (ie, 100% resolution of clinical signs for ≥ 30 days) or partial (ie, ≥ 50% but < 100% resolution of clinical signs for ≥ 30 days) responses. Cats reported to have < 50% improvement of clinical signs or responses of < 30 days were considered to be nonresponders. For cats with a response to treatment, remission duration was defined as the interval between the date of histopathologic diagnosis and progression or recurrence of clinical signs; nonresponders were not included in analysis of remission duration. Additional follow-up information was obtained via telephone conversations with owners and referring veterinarians. Cats still in remission at the last follow-up communication were included in analyses until the last day follow-up information was collected (and then censored). Overall survival time was defined as the time from the date of histopathologic diagnosis of low-grade lymphoma until death from any cause. Cats still alive at the last communication were censored on the last day of follow-up. Disease-specific survival was defined as time from histopathologic diagnosis until any death suspected or confirmed to be related to lymphoma; deaths attributed to concurrent diseases or unknown causes were included in analyses and then censored on the date of death (cats still alive were censored at the conclusion of the study).

Statistical analysis—Risk factors analyzed to determine their effect on response to treatment, remission duration, and overall survival time included anatomic location (gastrointestinal tract alone vs other organs with or without gastrointestinal tract involvement); age; weight; duration of clinical signs; sex (male vs female); and the following yes or no variables: vomiting, diarrhea, weight loss, anorexia, icterus, lethargy, hypocobalaminemia, and low serum folate concentration.

Frequencies of categoric variables potentially associated with initial response to treatment (type of remission achieved) were compared by use of the χ^2 test of independence and the Fisher exact test. The Kruskal-Wallis test was used for analysis of continuous variables. The Kaplan-Meier product-limit method was used to estimate remission duration, overall survival time, and disease-specific survival time. Kaplan-Meier remission duration and overall survival curves for each potential categoric risk factor were compared by the log-rank test for censored data. To evaluate the combined effects of potential risk factors on remission duration and survival, multivariable survival analysis was done by use of the Cox proportional hazards regression model. Variables with values of $P \leq 0.05$ in the univariable analyses were offered to the multivariable analyses. Models were chosen by backward elimination. All statistical calculations were performed with a commercially available software program,[c] and for the final analysis, 2-sided values of $P \leq 0.05$ were considered significant.

Results

Six hundred sixty-seven cats with lymphoma were initially identified by the retrospective search of medical records; 110 were coded as having low-grade lymphocytic lymphoma, and 557 were coded as having high-grade lymphoblastic lymphoma. Of the 110 cats with low-grade lymphoma, 69 were excluded for misdiagnosis (other neoplasia or nonneoplastic disease,

n = 15), slides of sections of biopsy specimens were missing or unavailable for histologic review (n = 7), no treatment was initiated or cats were treated with drugs other than prednisone and chlorambucil (16), and follow-up information was not found (31). On the basis of the retrospective search, low-grade histologic findings comprised 13% (88/667) of lymphomas of cats at our institutions.

Following necessary exclusions, 41 cats met all criteria to be included in the study. Twenty-four were males (1 intact, 23 castrated), and 17 were spayed females. Median age at diagnosis was 13 years (range, 6 to 17 years). Most cats were either domestic shorthair (n = 33) or domestic longhair (7); 1 cat was Manx. Median weight was 4.4 kg (9.7 lb) with a range of 1.9 to 7.2 kg (4.2 to 15.8 lb).

Duration of disease ranged from 5 days to 48 months (median, 6 months). Common clinical signs at the time of hospital admission included weight loss (34/41 [83%]), vomiting (30/41 [73%]), anorexia (27/41 [66%]), diarrhea (24/41 [59%]), and lethargy (16/41 [39%]). Three of 41 (7%) cats with lymphoma of the liver were icteric. Cats may have had > 1 clinical sign at the time of hospital admission.

Results of CBC determination and serum biochemical analysis were available for all cats. Medical records also included results of abdominal ultrasonography (40/41 [98%]), thoracic radiography (33/41 [80%]), FeLV and FIV tests (30/41 [73%]), and determination of serum cobalamin concentration (32/41 [78%]), serum folate concentration (27/41 [66%]), and serum trypsin-like immunoreactivity (16/41 [39%]).

Common abnormal results of clinicopathologic testing included low serum cobalamin concentrations in 25 of 32 (78%) cats tested, low serum folate concentrations in 1 of 27 (4%), high serum folate concentrations in 10 of 27 (37%), and increased trypsin-like immunoreactivity in 12 of 16 (75%). All cats with hypocobalaminemia had lymphoma of the small intestine. One of 3 cats without gastrointestinal tract involvement was tested for serum cobalamin concentration, the results of which were within reference range. Twenty-two cats with documented hypocobalaminemia received parenteral supplementation. However, treatment dose and frequency were highly inconsistent, and few cats had serum cobalamin concentrations rechecked. All cats tested for FeLV and FIV had negative results.

Twenty-one biopsy specimens were collected via gastroduodenal endoscopy, 15 were collected during laparotomy, 4 via laparoscopy, and 1 with an ultrasound-guided, percutaneous needle-core instrument. Lymphoma was confined to the gastrointestinal tract in 28 of 41 (68%) cats, whereas 13 of 41 (32%) cats had other organ systems affected with or without gastrointestinal tract involvement. Extragastrointestinal tract sites included mesenteric lymph nodes (n = 6), liver (10), spleen (1), and pancreas (1). Some cats had > 1 site affected. Eighty-nine percent (32/36) of lymphomas were determined to be of T-cell origin via immunohistochemistry, whereas 8% (3/36) were of B-cell origin. One cat had non–B-cell, non–T-cell low-grade lymphoma. As a result of insufficient amount of archived tissue, immunophenotype could not be determined in biopsy specimens of 5 cats (**Table 1**).

Thirty-one of 41 (76%) cats received prednisone at a dose of 5 mg, PO, every 12 to 24 hours, and 10 (24%) cats received prednisone at a dose of 10 mg, PO, every 24 hours. Thirty-five of 41 (85%) cats received chlorambucil at a dose of 2 mg, PO, every other day, and 6 (15%) cats received chlorambucil at a dose of 2 mg, PO, every third day.

Response to treatment—Information describing response to treatment was not available for 2 cats with lymphoma of the gastrointestinal tract, although duration of survival was known. Thirty-seven of the remaining 39 (95%) cats had a response to chemotherapy. As judged from the medical records, 56% (22/39) achieved a complete response and 39% (15/39) achieved a partial response. Of the cats with lymphoma of the gastrointestinal tract, 9 achieved a complete response and 16 achieved a partial response. Of the cats with lymphoma of nongastrointestinal tract sites, 6 achieved a complete response and 6 achieved a partial response. Two of 41 (5%) cats had no response to treatment and included 1 cat with low-grade lymphoma of the liver and 1 cat with low-grade lymphoma of the small intestine. No significant differences were found between responders and nonresponders or between cats achieving a complete response versus a partial response with respect to any of the 13 analyzed risk factors.

Remission duration and risk factors for relapse—Thirty-seven of the 39 cats with response information were judged to have responded to treatment and were included in the analysis of remission duration. Of the 37 responders, 13 relapsed or progressed during the follow-up period, which was either confirmed with repeat histologic evaluation of biopsy specimens or clinically determined on the basis of recurrence of signs. Twenty-four cats were still under observation (until remission ended or the cat was lost to follow-up) at a median of 383 days (range, 44 to 2,010 days). Analysis of censored survival curves indicated that the overall median remission duration was 948 days (lower 95% CL, 484 days; upper CL, undefined). Risk factors significantly associated with short remission duration when evaluated in-

Table 1—Frequencies of sites affected in 41 cats with low-grade lymphoma.

		Immunophenotype*	
Sites affected	**Total No. of cases**	**T-cell**	**B-cell**
SI only	25	20	1
SI, liver	3	3	0
SI, liver, mesenteric LN†	3	1	0
Stomach, SI	2	2	0
SI, mesenteric LN	2	2	0
Liver only	2	2	0
Stomach only	1	0	1
Stomach, SI, liver	1	1	0
Liver, spleen, mesenteric LN	1	0	1
SI, pancreas	1	1	0

SI = Small intestine. LN = Lymph nodes.
*Not all cats had immunophenotyping performed. †Immunophenotyping revealed non–T-cell, non–B-cell lymphoma in 1 cat.

Table 2—Variables associated with remission duration among 37 cats with low-grade lymphoma that responded to treatment with oral administration of prednisone and chlorambucil, as determined by univariable analysis.

Variable	No. of cats	Median remission duration (d)	*P* value (log-rank)
Response to treatment*			0.031
Complete	22	897	
Partial	15	428	
Anatomic location			0.028
Gastrointestinal only	25	963	
Other sites ± gastrointestinal	12	636	
Hypocobalaminemia			0.026
No	6	Not reached	
Yes	23	657	

*Assessed by the examining clinician and categorized as complete (100% resolution of clinical signs for ≥ 30 days) or partial (≥ 50% but < 100% resolution of clinical signs for ≥ 30 days).

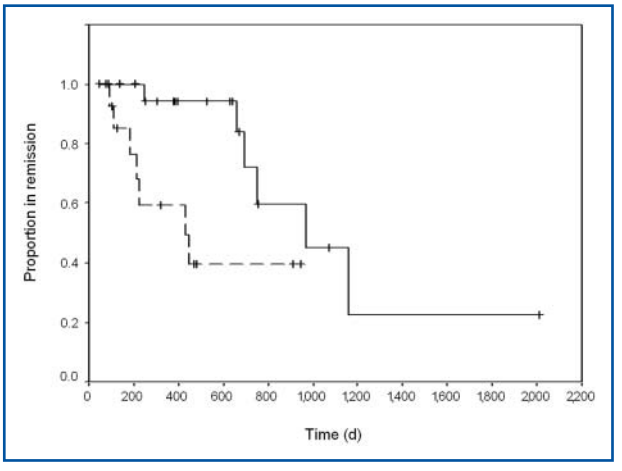

Figure 1—Kaplan-Meier curve depicting remission duration for 22 cats with lymphocytic lymphoma that achieved a complete response to treatment (solid line) and 15 cats that achieved partial response to treatment (broken line). Median remission duration for cats achieving a partial response to treatment (428 days) was significantly ($P = 0.031$) shorter than the median remission duration for cats achieving a complete response to treatment (897 days). Vertical marks represent censored cats.

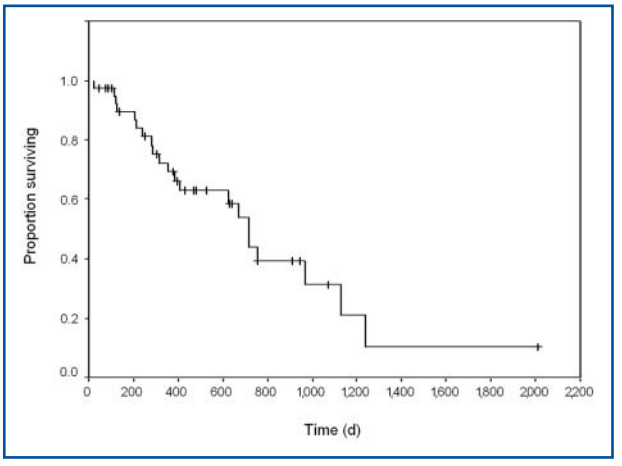

Figure 2—Kaplan-Meier curve depicting overall survival time for 41 cats with low-grade lymphoma treated with prednisone and chlorambucil. In the overall survival analysis, deaths from any cause were considered endpoints of survival. The overall median survival time was 704 days (95% CI, 383 to 1,237 days).

dividually were determined (**Table 2**). In multivariable analysis, only response to treatment was significantly associated with remission duration. Cats that had a partial response to treatment had a 4.3 times greater hazard of having progression of clinical signs than were cats that achieved a complete response (95% CI, 1.2 to 16; $P = 0.002$). The median remission duration of 15 cats with a partial response was 428 days (lower 95% CL, 183 days; upper CL, undefined), and the median remission duration of 22 cats with a complete response was 897 days (lower 95% CL, 695 days; upper CL, undefined; **Figure 1**). In this multivariable calculation, an interrelationship involving serum cobalamin concentration was suspected because the log-likelihood changed significantly when the latter variable was removed (although the *P* value for serum cobalamin concentration was 0.45). In the statistical analysis, response to treatment was therefore adjusted for serum cobalamin concentration.

Survival time and risk factors for death—Twenty-one cats were known to have died during the follow-up period; 12 cats were confirmed (n = 1) or suspected (11) to have died from low-grade lymphoma, and the remaining 9 cats died of concurrent diseases (2) or unknown causes (7). Twenty cats were lost to follow-up or were still alive at the conclusion of the study (median time under observation was 476 days; range, 44 to 2,010 days). The overall survival curve analysis indicated that the median survival time was 704 days (95% CI, 383 to 1,237 days; **Figure 2**). Median overall survival times for cats with lymphocytic lymphoma of the gastrointestinal tract and lymphocytic lymphoma of nongastrointestinal tract sites were 765 and 714 days, respectively ($P = 0.48$). None of the other evaluated risk factors was significantly associated with overall survival. Three cats that died had complete necropsy examinations performed. One cat was confirmed to have died from recurrent lymphoma of the liver, 1 cat died of hepatic lipidosis and concurrent immune-mediated hemolytic anemia, and 1 cat died of a large parathyroid tumor and associated hypercalcemia. The median disease-specific survival time was 967 days (95% CI, 593 to 1,341 days).

Discussion

On the basis of the results of our study, the prognosis for cats with low-grade lymphocytic lymphoma treated with prednisone and chlorambucil is favorable. Ninety-two percent of cats responded to treatment for a median of > 2.5 years. A large number cats identified during the retrospective search of medical records were excluded from the study as a result of inadequate follow-up information, and this might have biased the assessment of outcome.

On the basis of the retrospective search of medical records from our institutions, low-grade lymphocytic histologic findings represented approximately 13% of all cats with lymphoma. Results of other studies[1-4] indicate a similar frequency. To our knowledge, this is the largest study to evaluate outcome of cats with this histologic form of lymphoma affecting the gastrointestinal tract or other organ systems. In 1 study,[7] 29 cats with low-grade lymphoma were treated with prednisone (10 mg, PO)

once daily and chlorambucil (15 mg/m^2 body surface area, PO) for 4 days every 3 weeks and responded for a median of 16 months. All cats were considered to have disease confined to the gastrointestinal tract.[7] Complete clinical staging, however, was not done. For example, only 7 cats were evaluated by use of ultrasonography.[7] Other studies[2,4-6,11] of cats with lymphoma include populations with low-, intermediate-, and high-grade subtypes affecting multiple organ systems and report outcome after treatment with protocols generally designed for patients with biologically aggressive disease, leading to imprecise information about the prognosis of this distinct histologic form.

The chemotherapy protocol (prednisone and chlorambucil) was administered PO on an outpatient basis. The rationale behind treating cats with lymphocytic lymphoma with a less-intensive chemotherapy regimen was first proposed by Fondacaro et al,[7] who suggested that the slow progression of this low-grade disease warrants treatment with cytotoxic agents that are more commonly used for indolent neoplasms.[12]

Anatomic location was not prognostic for response to treatment, response duration, or overall survival time. The number of cats with disease affecting nongastrointestinal tract sites such as the liver, spleen, or pancreas, however, was small, and statistical power to detect a difference would be low. In contrast to Fondacaro et al,[7] a thorough clinical evaluation (eg, hematologic tests, radiography, and ultrasonography) was done in most of our cats. Nonetheless, low levels of disease might still have been missed. Also, various techniques were used for biopsy specimen collection and were not done for all organs. Endoscopy only allowed for biopsy of the stomach and duodenum, and during laparotomy, organs might have been selected for biopsy on the basis of hematologic results or abnormal appearance. This could have resulted in underestimation of the true extent of disease in some patients, and we recognize that this is a limitation of our study.

Fondacaro et al[7] found clinical signs of vomiting, anorexia, and lethargy to be prognostic for outcome in cats with lymphocytic lymphoma of the gastrointestinal tract. Of the factors analyzed in our study, a partial response to treatment with prednisone and chlorambucil was associated with shorter response duration. For 22 cats with a complete response to treatment, the median response duration was 29 months, compared with 14 months for 15 cats with a partial response to treatment. Response to chemotherapy has been the main factor with consistent prognostic value throughout many prior studies[4,6,11,13-15] of cats with high-grade lymphoma. In another report[7] of cats with lymphocytic lymphoma similarly treated, cats that achieved a complete response had significantly greater survival times than those that did not achieve complete remission. In our study, however, response to treatment did not have any association with overall survival time. In most instances, only clinical signs as recorded in medical records were used to judge response to treatment. A standardized scoring system and objective assessment of remission status were not available. Only sporadic follow-up imaging via abdominal ultrasonography and thoracic radiography was performed, and repeat biopsy specimens were only collected in a few instances when patients were thought to be having a relapse. Additional studies evaluating alternative treatments to improve outcome of cats with signs that fail to completely resolve with treatment, and perhaps for cats that have recurrence of clinical signs after an initial complete response, nonetheless, might still be warranted. For example, in the report by Fondacaro et al,[7] cats with low-grade lymphoma treated PO with cyclophosphamide after relapse had significantly longer survival time, compared with cats that did not receive any rescue drugs after relapse.

In our study, 78% of cats tested had hypocobalaminemia, which was associated with a short remission duration, but only in the univariable analysis. Cobalamin (vitamin B_{12}) is absorbed exclusively in the ileum, as complex of cobalamin and intrinsic factor, and is a cofactor in several important enzymatic reactions.[16] Cats with various digestive diseases, including lymphoma of the intestine, inflammatory bowel disease, pancreatitis, and cholangiohepatitis or cholangitis, have serum cobalamin concentrations less than the reference limit.[16] These deficits often accompany clinical signs of gastrointestinal tract disturbance (eg, weight loss, diarrhea, vomiting, and inappetence),[16] and cats with severe hypocobalaminemia (< 100 ng/L) have substantial metabolic consequences and low concentrations of several downstream amino acids.[17] Some cats with hypocobalaminemia in our study received parenteral supplementation. However, treatment dose and frequency were not standardized and few cats had serum cobalamin concentration rechecked (precluding analysis). Most cats that receive parenteral supplementation should have improvement in serum cobalamin concentrations[16,18] and some cats might regain ability to absorb dietary cobalamin as the primary disease process is effectively treated.[16] Consistent reevaluation of serum cobalamin concentrations would help to determine the indication for additional supplementation and might be an indicator of relapse of disease in some cats.

Thirty-seven percent of cats had high serum folate concentrations. Folate is absorbed in the proximal small intestine, and finding unusually high serum folate concentrations may be related to variable dietary folate concentrations, alteration in the small intestinal bacterial flora, or a decrease in the use of folate with simultaneous cobalamin deficiency.[19]

Duration of clinical signs prior to histopathologic diagnosis of low-grade lymphoma ranged from days to 4 years (median, 6 months). Cats with chronic signs of gastrointestinal tract disease are often presumptively given a diagnosis of inflammatory bowel disease. Previous investigators, however, have failed to distinguish inflammatory bowel disease from lymphoma of the gastrointestinal tract on the basis of clinical signs, physical examination findings, or other noninvasive diagnostics.[20] Progression of chronic inflammatory bowel disease to lymphoma of the intestine is well documented for humans.[21] A similar sequence of events in cats, however, remains anecdotal.[20]

Half of the biopsy specimens in our study were collected via endoscopy. Endoscopically obtained biopsy specimens are useful for diagnosis of lymphoma of the stomach but are not considered adequate for differen-

tiating between inflammatory bowel disease and lymphoma of the small intestine.[20] The discrepancy is more often an incorrect diagnosis of inflammatory bowel disease when truly the patient has lymphoma. In 1 study,[20] however, 2 of 12 cats with a diagnosis of inflammatory bowel disease on the basis of histologic evaluation of full-thickness gastrointestinal biopsy specimens were incorrectly given a diagnosis of lymphoma when histologic evaluation was limited to only endoscopically obtained biopsy specimens. It cannot be excluded that cats in our study were similarly given misdiagnoses. Cell-phenotype analysis was performed, but results only assist in classifying groups of lymphomas or lymphoid tissues, not in confirming neoplasia. For example, expansion of T-cell populations can occur in mucosal-associated lymphoid tissue of the small intestine in inflammatory bowel disease of cats.[22] Future studies of cats with lymphoma confirmed by examination of full-thickness biopsy specimens or perhaps other criteria for the diagnosis of neoplasia such as molecular clonality are indicated.[22,23]

Results of our study support the use of oral administration of prednisone and chlorambucil as an effective treatment regimen for most cats with low-grade lymphocytic lymphoma. Despite shorter remission duration, cats with only a partial resolution of clinical signs still had long survival times. Anatomic area affected and hypocobalaminemia were not associated with outcome, but histologic evaluation of biopsy specimens systematically obtained from organs and measuring serum cobalamin concentrations of additional cats should be done.

a. PrednisTab, Lloyd Inc, Shenandoah, Iowa.
b. Leukeran, GlaxoSmithKline, Research Triangle Park, NC.
c. Statistix 8, 2003, Analytical Software, Tallahassee, Fla.

References

1. Valli VE, Jacobs RM, Norris A, et al. The histologic classification of 602 cases of feline lymphoproliferative disease using the National Cancer Institute working formulation. *J Vet Diagn Invest* 2000;12:295–306.
2. Mahony OM, Moore AS, Cotter SM, et al. Alimentary lymphoma in cats: 28 cases (1988–1993). *J Am Vet Med Assoc* 1995;207:1593–1598.
3. Gabor LJ, Malik R, Canfield PJ. Clinical and anatomical features of lymphosarcoma in 118 cats. *Aust Vet J* 1998;76:725–732.
4. Milner RJ, Peyton J, Cooke K, et al. Response rates and survival times for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol: 38 cases (1996–2003). *J Am Vet Med Assoc* 2005;227:1118–1122.
5. Carreras JK, Goldschmidt M, Lamb M, et al. Feline epitheliotropic intestinal malignant lymphoma: 10 cases (1997–2000). *J Vet Intern Med* 2003;17:326–331.
6. Dank G, Lucroy MD, Griffey SM, et al. bcl-2 and MIB-1 labeling indexes in cats with lymphoma. *J Vet Intern Med* 2002;16:720–725.
7. Fondacaro JV, Richter KP, Carpenter JL, et al. Feline gastrointestinal lymphoma: 67 cases (1988–1996). *Eur J Comp Gastroenterol* 1999;4:5–11.
8. Valli VE, Jacobs RM, Parodi AL, et al. *Histological classification of hematopoietic tumors of domestic animals*. 2nd ed. Washington, DC: Armed Forces Institute of Pathology, 2002;39–46.
9. Ben-Ezra J. Small lymphocytic lymphoma. In: Knowles DM, ed. *Neoplastic hematopathology.* 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 2001;773–778.
10. McDonough SP, Van Winkle TJ, Valentine BA, et al. Clinicopathological and immunophenotypical features of canine intravascular lymphoma (malignant angioendotheliomatosis). *J Comp Pathol* 2002;126:277–288.
11. Cotter SM. Treatment of lymphoma and leukemia with cyclophosphamide, vincristine, and prednisone: II. Treatment of cats. *J Am Anim Hosp Assoc* 1983;19:166–172.
12. Tew KD, Colvin OM, Chabner BA. Alkylating agents. In: Chabner BA, Longo DL, eds. *Cancer chemotherapy and biotherapy: principles and practice*. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins, 2001;374–414.
13. Vail DM, Moore AS, Ogilvie GK, et al. Feline lymphoma (145 cases): proliferation indices, cluster of differentiation 3 immunoreactivity, and their association with prognosis in 90 cats. *J Vet Intern Med* 1998;12:349–354.
14. Teske E, van Straten G, van Noort R, et al. Chemotherapy with cyclophosphamide, vincristine, and prednisolone (COP) in cats with malignant lymphoma: new results with an old protocol. *J Vet Intern Med* 2002;16:179–186.
15. Zwahlen CH, Lucroy MD, Kraegel SA, et al. Results of chemotherapy for cats with alimentary malignant lymphoma: 21 cases (1993–1997). *J Am Vet Med Assoc* 1998;213:1144–1149.
16. Simpson KW, Fyfe J, Cornetta A, et al. Subnormal concentrations of serum cobalamin (vitamin B12) in cats with gastrointestinal disease. *J Vet Intern Med* 2001;15:26–32.
17. Ruaux CG, Steiner JM, Williams DA. Metabolism of amino acids in cats with severe cobalamin deficiency. *Am J Vet Res* 2001;62:1852–1858.
18. Ruaux CG, Steiner JM, Williams DA. Early biochemical and clinical responses to cobalamin supplementation in cats with signs of gastrointestinal disease and severe hypocobalaminemia. *J Vet Intern Med* 2005;19:155–160.
19. Davenport DJ, Ching RJ, Hunt JH, et al. The effect of dietary levels of folate and cobalamin on the serum concentration of folate and cobalamin in the dog. *J Nutr* 1994;124:2559S–2562S.
20. Evans SE, Bonczynski JJ, Broussard JD, et al. Comparison of endoscopic and full-thickness biopsy specimens for diagnosis of inflammatory bowel disease and alimentary tract lymphoma in cats. *J Am Vet Med Assoc* 2006;229:1447–1450.
21. Verkarre V, Asnafi V, Lecomte T, et al. Refractory coeliac sprue is a diffuse gastrointestinal disease. *Gut* 2003;52:205–211.
22. Moore PF, Woo JC, Vernau W, et al. Characterization of feline T cell receptor gamma (TCRG) variable region genes for the molecular diagnosis of feline intestinal T cell lymphoma. *Vet Immunol Immunopathol* 2005;106:167–178.
23. Werner JA, Woo JC, Vernau W, et al. Characterization of feline immunoglobulin heavy chain variable region genes for the molecular diagnosis of B-cell neoplasia. *Vet Pathol* 2005;42:596–607.