

# Response rates and survival times for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol: 38 cases (1996–2003)

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**Objective**—To determine response rates and survival times for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol.

**Design**—Retrospective study.

**Animals**—38 cats with lymphoma.

**Procedure**—Medical records were reviewed, and information on age, sex, breed, FeLV and FIV infection status, anatomic form, clinical stage, and survival time was obtained. Immunophenotyping was not performed.

**Results**—Mean  $\pm$  SD age of the cats was  $10.9 \pm 4.4$  years. Overall median survival time was 210 days (interquartile range, 90 to 657 days), and overall duration of first remission was 156 days (interquartile range, 87 to 316 days). Age, sex, anatomic form, and clinical stage were not significantly associated with duration of first remission or survival time. Eighteen of the 38 (47%) cats had complete remission, 14 (37%) had partial remission, and 6 (16%) had no response. Duration of first remission was significantly longer for cats with complete remission (654 days) than for cats with partial remission (114 days). Median survival time for cats with complete remission (654 days) was significantly longer than median survival time for cats with partial remission (122 days) and for cats with no response (11 days).

**Conclusions and Clinical Relevance**—Results suggested that a high percentage of cats with lymphoma will respond to treatment with the University of Wisconsin-Madison chemotherapy protocol. Age, sex, anatomic form, and clinical stage were not significantly associated with duration of first response or survival time, but initial response to treatment was. (*J Am Vet Med Assoc* 2005;227:1118–1122)

Several chemotherapy protocols for the treatment of cats with lymphoma have been described.<sup>1–13</sup> However, comparing published outcomes of the various chemotherapeutic protocols is often difficult, either because of potential bias in patient selection<sup>2,5,7</sup> or because of differences in confounding factors, such

as geographic location, FeLV and FIV infection status, and anatomic and clinical stage, among studies.<sup>2,5,8–11,14</sup>

For several years, the University of Florida has used a protocol incorporating vincristine, L-asparaginase, prednisone, cyclophosphamide, doxorubicin, chlorambucil, and methotrexate for the treatment of cats with lymphoma. This protocol was developed at the University of Wisconsin-Madison (UWM) and first described in 1996.<sup>15</sup> However, to our knowledge, the only study<sup>3</sup> reporting outcome of cats treated with this protocol combined cats treated with this protocol with cats treated with a variety of other chemotherapy protocols. Thus, little information is available on outcome of cats treated with this particular chemotherapy protocol. The purpose of the study reported here, therefore, was to determine response rates and survival times for cats with lymphoma treated with the UWM chemotherapy protocol.

## Criteria for Selection of Cases

Medical records of cats examined at the University of Florida College of Veterinary Medicine or the All Cats Healthcare Clinic in Gainesville, Fla, between 1996 and 2003 because of lymphoma were reviewed. Cats were included in the study if the diagnosis had been confirmed by means of cytologic or histologic examination, the UWM chemotherapy protocol had been used, and the medical record was complete.

## Procedures

Information obtained from the medical records included age, breed, sex, results of tests for FeLV and FIV infection, date when the diagnosis was confirmed, anatomic form, clinical stage, initial response to chemotherapy, duration of remission, and survival time. When applicable, information on tumor volume was also recorded. Anatomic form was classified as alimentary, mediastinal, multicentric, or extranodal. Clinical stage was determined on the basis of standard criteria (Appendix 1).<sup>1</sup>

All cats were treated with the UWM chemotherapy protocol (Appendix 2). During each follow-up visit, cats were classified as having complete remission (CR), partial remission (PR), or no response (NR). For cats with measurable tumors, CR was defined as regression of all measurable disease and clinical signs, PR was defined as a decrease of  $> 50\%$  but  $< 100\%$  in the sum of the products of the perpendicular diameters of all measurable tumors, and NR was defined as a decrease of  $< 50\%$  or an increase in the sum of the products of

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the perpendicular diameters of all measurable tumors. Because cats with alimentary lymphoma typically did not have measurable tumors, modified criteria were used to determine the response to treatment. For cats with a palpable gastrointestinal tract mass and thoracic effusion, CR was defined as resolution of the thoracic effusion and a reduction in size of the gastrointestinal tract mass so that it was no longer palpable, PR was defined as a reduction in size of the gastrointestinal tract mass although the mass was still palpable, and NR was classified as no change in size of the gastrointestinal tract mass or severity of the thoracic effusion. Cats with diffuse alimentary lymphoma typically had large, palpable mesenteric lymph nodes, and response to treatment was determined on the basis of resolution of these masses and improvement in clinical signs.

**Statistical analyses**—Descriptive statistics were calculated for age, sex, FeLV and FIV infection status, anatomic form, and clinical stage, and the Kolmogorov-Smirnov test was used to determine whether data were normally distributed and variances were equal. A 1-way ANOVA (parametric data) or 1-way ANOVA on ranks (nonparametric data) was used to determine whether age was associated with sex, breed, FeLV infection status, anatomic form, or clinical stage. Groups that consisted of only 1 or 2 cases were excluded from analyses.

Duration of treatment was calculated from the date of first treatment until the protocol was discontinued. Because cats with lymphoma are never, strictly speaking, free from disease following treatment, disease-free interval was not calculated. Rather, the duration of first remission was determined. The duration of first remission (and duration of second remission) was defined as the time from achievement of the best response (CR or PR) following initiation of chemotherapy to the time of relapse (ie, in the case of CR, return of clinical detectable disease, and in the case of PR, an increase in the size of a previously detectable disease or new disease). Survival time was calculated as the time from confirmation of the diagnosis to the time of death. The Kaplan-Meier product-limit method was used to analyze data for duration of first remission and survival time. The log-rank test was used to compare duration of first remission between cats that had CR and cats that had PR and to compare survival time among cats that had CR, cats that had PR, and cats that had NR. The log-rank test was also used to examine the effects of age, sex, anatomic form, and clinical stage on duration of first remission and survival time. For analysis of duration of first remission, cats were censored if relapse had not occurred before the end of the study period, the cat was lost to follow up, or the cat died before relapse occurred. For analysis of survival time, cats were censored if they were lost to follow up, died of causes other than lymphoma, or were still alive at the end of the study period.

Parametric data are reported as mean  $\pm$  SD, and nonparametric data are reported as median and interquartile range (IQR; the 25th to 75th percentile). For all analyses, standard statistical software<sup>a</sup> was used; values of  $P < 0.05$  were considered significant.

## Results

**Demographic information**—The initial search of the medical records identified 104 cats examined because of lymphoma during the study period. Thirty-nine of the 104 (38%) cats did not receive any treatment; 15 (14%) were treated with a cyclophosphamide, vincristine, and prednisone protocol; 10 (10%) were treated only with prednisone; and 40 (38%) were treated with the UWM chemotherapy protocol. Two of the cats treated with the UWM protocol did not meet the inclusion criteria. Therefore, 38 cats were included in the study.

Of the 38 cats, 30 were examined and treated at the University of Florida. The remaining 8 were treated at the All Cats Healthcare Clinic. However, in all 8 of these cats, the diagnosis had been confirmed at the University of Florida.

Mean  $\pm$  SD age of the 38 cats included in the study was  $10.9 \pm 4.4$  years (range, 1 to 21 years; **Figure 1**). Twenty-two (57%) cats were male (21 were neutered), and 16 (43%) were female (all were neutered). There were 27 (71%) domestic shorthair cats, 7 (18%) domestic longhair cats, 2 (5%) Siamese, 1 (3%) Maine Coon, and 1 (3%) domestic medium hair cat. Thirty-one cats were tested for FeLV and FIV infection. Only 3 (10%) were positive for FeLV infection, and 2 (6%) were positive for FIV infection. None of the cats with FeLV infection had mediastinal lymphoma; rather, 2 had alimentary lymphoma and 1 had multicentric lymphoma.

Sixteen (42%) cats had alimentary lymphoma, with 7 classified as having predominately small lymphocytes and 4 classified as having predominately large lymphocytes (cell type was not reported for the remaining 5 cats). Eleven (28%) cats had multicentric lymphoma, 9 (24%) had extranodal lymphoma, and 2 (5%) had mediastinal lymphoma. Four of the 9 cats with extranodal lymphoma had CNS involvement, 3 had renal involvement, and 2 had involvement of other systems.

Sixteen (43%) cats had stage III lymphoma, 10 (26%) had stage I lymphoma, 8 (21%) had stage IV lymphoma, 2 (5%) had stage II lymphoma, and 2 (5%)

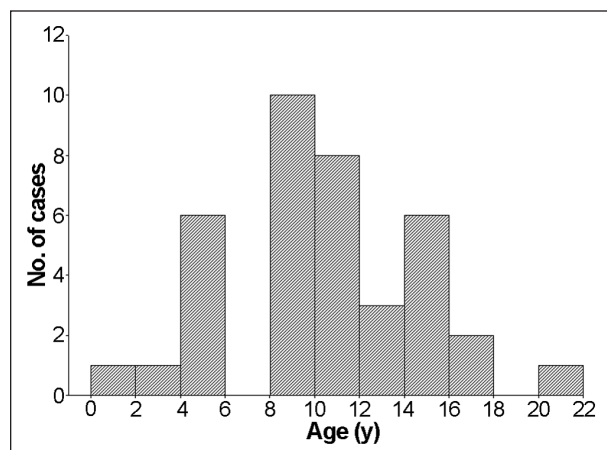


Figure 1—Age distribution of 38 cats treated for lymphoma at the University of Florida College of Veterinary Medicine or the All Cats Healthcare Clinic in Gainesville, Fla, between 1996 and 2003.

had stage V lymphoma. Age was not significantly associated with sex, breed, anatomic form, or clinical stage.

**Outcome**—Age, sex, anatomic form, and clinical stage were not significantly associated with duration of first remission or survival time. There were too few cats with FeLV infection ( $n = 3$ ) to determine whether this factor was associated with duration of first remission or survival time.

For all 38 cats, median duration of treatment was 124 days (IQR, 58 to 283 days). Overall median duration of first remission was 156 days (IQR, 87 to 316 days), and overall median survival time was 210 days (IQR, 90 to 657 days).

Eighteen of the 38 (47%) cats had CR, 14 (37%) had PR, and 6 (16%) had NR. Median time to first remission for cats with CR (14 days; IQR, 10 to 22 days) was the same as median time to first remission for cats with PR (14 days; IQR, 14 to 24 days). Duration of first remission was significantly ( $P < 0.001$ ) longer for cats with CR (654 days; IQR, 266 to 1,137 days) than for cats with PR (114 days; IQR, 8 to 158 days; **Figure 2**).

Four of the 18 cats with CR did not have clinical signs of a relapse before the end of the study period or died of causes other than lymphoma before a relapse occurred. The remaining 14 cats with CR were all documented to have had a relapse. Eight of these were euthanatized immediately after relapse was documented. In the remaining 6, the chemotherapy protocol was restarted from the beginning, and all 6 had a second remission.

One of the 14 cats with PR died of causes other than lymphoma before a relapse occurred. The remaining 13 cats with PR were all documented to have had a relapse. Seven of these were euthanatized immediately after relapse was documented. In the remaining 6, the chemotherapy protocol was restarted from the beginning, and 4 of the 6 had a second remission. Median duration of the second remission was significantly ( $P = 0.009$ ) longer for cats that had originally had CR (142 days; IQR, 122 to 428 days) than for cats that had originally had PR (30.5 days; IQR, 14 to 82 days).

Median survival time for cats with CR (654 days; IQR, 433 to 1,222 days; **Figure 3**) was significantly ( $P = 0.009$ ) longer than median survival time for cats with PR (122 days; IQR, 108 to 210 days). Median survival times for cats with CR and for cats with PR were both significantly ( $P < 0.009$ ) longer than median survival time for cats with NR (11 days; IQR, 11 to 42 days).

**Adverse effects**—Because gastrointestinal tract abnormalities in cats with alimentary lymphoma were not consistently recorded, it was not possible to determine whether gastrointestinal tract toxicoses developed following initiation of chemotherapy. Hematologic toxicoses (neutrophil count  $< 2.5 \times 10^3$  cells/ $\mu\text{L}$ ) resulted in treatment delays in 13 (34%) cats; treatment delays typically ranged from 5 to 7 days. Recurrent neutropenia following administration of the same drug resulted in reduction of subsequent doses by 25%.

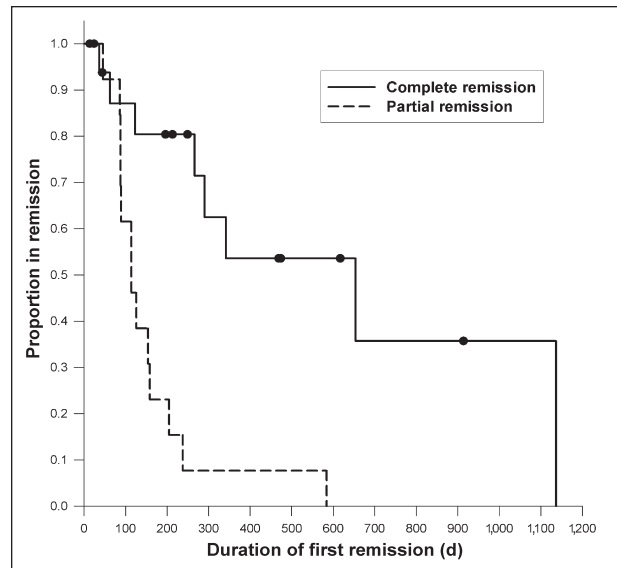


Figure 2—Kaplan-Meier graphs of duration of first remission for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol that had a complete or partial remission. Circles represent censored observations.

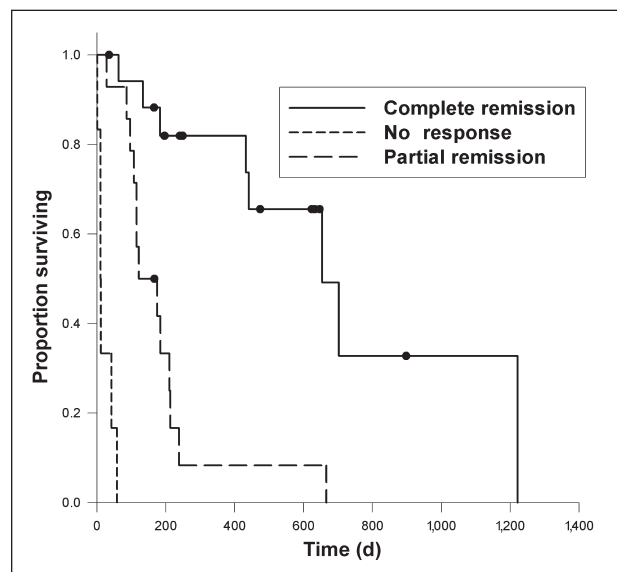


Figure 3—Kaplan-Meier graphs of survival time for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol that had a complete or partial remission or no response to treatment. Circles represent censored observations.

## Discussion

Results of the present study suggest that approximately 84% of cats with lymphoma will respond following treatment with the UWM chemotherapy protocol, with an overall median survival time of 210 days. Age, sex, anatomic form, and clinical stage were not significantly associated with duration of first response or survival time in the present study. However, the initial response to treatment was significantly associated both with duration of first remission and with survival time. Median duration of first remission was significantly longer for cats with CR than for cats with PR, and median survival time was significantly longer for cats with CR than for cats with PR or cats with NR.

Demographics of cats included in the present study were similar to those reported previously.<sup>12</sup> Surprisingly, of 104 cats examined because of lymphoma during the study period, 39 (38%) were not treated. Although reasons why these cats were not treated could not consistently be determined from the medical records, it is possible that owners declined treatment because of severe clinical signs or FeLV infection.

Mean age of cats in the present study was 10.9 years (range, 1 to 21 years), which was similar to values reported in recent studies<sup>2,16,17</sup> and supports the suggestion that there has been a shift in the mean age of cats with lymphoma, from 4 to 6 years of age in earlier reports<sup>1,4,6</sup> to 9 to 11 years more recently. Consistent with findings in other studies,<sup>2,3</sup> most cats in the present study were domestic shorthairs.

Previous studies<sup>1,3,9,13</sup> have suggested that cats with FeLV infection that develop lymphoma typically, although not exclusively, develop the mediastinal form, with signs developing at a young age. In contrast, none of the 3 cats with positive FeLV test results in the present study had mediastinal lymphoma and none were particularly young. Because there were so few cats with positive FeLV test results, we were not able to determine whether FeLV infection adversely affected survival time. However, FeLV infection has previously been reported to have a negative effect on survival time.<sup>1,3,9,13</sup>

In the present study, only 2 of 31 (6%) cats had positive FIV test results. In contrast, a study<sup>18</sup> from Australia reported that 50% of cats with lymphoma had FIV infection, possibly because of the higher prevalence of FIV infection in Australia. In previous studies<sup>4,10,19,20</sup> in the United States, the percentage of FIV-infected cats that had lymphoma has ranged from 0% to 15%.

In earlier studies,<sup>1,4,6</sup> mediastinal lymphoma was the most common anatomic form of lymphoma in cats, with 40% to 50% of affected cats having the mediastinal form. In the present study, however, only 2 (6%) cats had mediastinal lymphoma, and alimentary lymphoma was the most common anatomic form, in agreement with findings from more recent studies.<sup>3,17</sup> Mean age of cats with alimentary lymphoma in the present study was 10.2 years, which was similar to mean age reported in previous studies<sup>3,10,20</sup> and supports the suggestion that alimentary lymphoma is more common in older cats. Cats with mediastinal lymphoma in the present study were 3 and 11 years old, which was similar to findings in previous studies.<sup>3,16</sup> Multicentric lymphoma was identified in 11 (28%) cats in the present study, which was comparable to percentages in previous studies.<sup>3,6</sup> Extranodal lymphoma was identified in 9 (24%) cats in the present study.

Clinical stage was not found to be a significant prognostic factor in the present study, in contrast to results of previous studies<sup>1,3,6</sup> in which cats with stage I or II lymphoma had significantly longer remission and survival times. Most cats in the present study had stage III (16 [43%]) or stage I (10 [26%]), which was similar to the distribution in a previous study.<sup>3</sup>

Results of the present study seem to suggest that the proportion of cats that can be expected to have CR following treatment with the UWM chemotherapy protocol

(18/38 [47%]) may be lower than proportions reported in previous studies<sup>2,3</sup> in which cats were treated with a protocol involving cyclophosphamide, vincristine, and prednisone (64% and 75%). However, both of these previous studies included substantial numbers of cats with mediastinal lymphoma, although the percentage of cats with positive FeLV test result was low (7.4%) in 1 study<sup>2</sup> and not reported in the other.<sup>3</sup> Two other studies<sup>5,7</sup> reported CR rates for cats with lymphoma treated with cyclophosphamide, vincristine, and prednisone (32% and 47%) that were similar to the rate in the present study. A separate study<sup>1</sup> reported a CR rate of 62% for cats with lymphoma treated with vincristine, cyclophosphamide, methotrexate, and L-asparaginase, but this study had a high proportion of cats with positive FeLV test results (51%), making comparisons difficult. Studies<sup>8,10</sup> of cats treated with a protocol similar to the UWM protocol reported CR rates of 80% and 38%. However, the study<sup>10</sup> with the lower rate only included cats with alimentary lymphoma, illustrating the difficulties associated with comparing results of different studies. Unfortunately, the only previous study<sup>3</sup> in which cats were treated with the UWM protocol did not provide response rates for this subgroup of cats.

In the present study, median time to remission was 14 days both for cats with CR and for cats with PR. Although time to remission was not significantly different between groups, duration of first remission, duration of second remission, and survival time were. Similarly, several recent studies<sup>2,3,8,10,13</sup> have reported significant differences in remission duration and survival time between cats with CR versus PR, which seems to lend support to the suggestion that tumors in these cats are sensitive to chemotherapy from the outset or they are not. Unfortunately, immunophenotyping to identify susceptible subpopulations was not done in the present study.

Limitations of the present study include potential biases in case selection; low case numbers, particularly in certain groups (eg, mediastinal lymphoma, stages II and V, and FeLV positive); the lack of a control group; and the inability to verify accuracy of case records. Case selection was biased by the high percentage of owners who were unwilling to treat their cats, and the low numbers of cats in certain groups prevented multivariate analyses of the data. Because the number of cats treated for lymphoma is low, compared with the number of dogs, it was difficult to accumulate a large number of cases over a reasonable study period.

a. SigmaStat for Windows, version 3.00, and SigmaPlot for Windows, version 8.02, SPSS Inc, Chicago, Ill.

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## Appendix 1

Criteria for determining clinical stage in cats with lymphoma.

Stage	Description
I	Single tumor (extranodal) or anatomic area (nodal); includes primary thoracic tumors
II	Single tumor with regional lymph node involvement; 2 or more nodal areas on the same side of the diaphragm;
2	single tumors with or without regional lymph node involvement on the same side of the diaphragm; or resectable primary gastrointestinal tract tumor, with or without involvement of associated mesenteric lymph nodes
III	Two single tumors on opposite sides of the diaphragm; 2 or more nodal areas on opposite sides of the diaphragm; extensive, primary, unresectable intra-abdominal disease; or paraspinal or epidural tumor, regardless of other tumor sites
IV	Stage I, II, or III with involvement of liver, spleen, or both
V	Stage I, II, III, or IV with initial involvement of CNS, bone marrow, or both

## Appendix 2

Summary of the University of Wisconsin-Madison chemotherapy protocol for treatment of cats with lymphoma.

Week No.	Drugs and dosages
1	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once) L-Asparaginase (400 U/kg [182 U/lb], SC, once) Prednisone (2 mg/kg [0.9 mg/lb], PO, q 24 h)
2	Cyclophosphamide (200 mg/m <sup>2</sup> , IV, once) Prednisone (2 mg/kg, PO, q 24 h)
3	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once) Prednisone (1 mg/kg [0.45 mg/lb], PO, q 24 h)
4	Doxorubicin (25 mg/m <sup>2</sup> or 1 mg/kg, IV, once, as an infusion over 20 minutes) Prednisone (1 mg/kg, PO, q 48 h)*
6	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once)
7	Cyclophosphamide (200 mg/m <sup>2</sup> , IV, once)
8	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once)
9	Doxorubicin (25 mg/m <sup>2</sup> or 1 mg/kg, IV, once, as an infusion over 20 minutes)
11	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once)
13	Chlorambucil (1.4 mg/kg [0.64 mg/lb], PO, once)
15	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once)
17	Methotrexate (0.5 to 0.8 mg/kg [0.23 to 0.36 mg/lb], IV, once)
19	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once)
21	Chlorambucil (1.4 mg/kg, PO, once)
23	Vincristine (0.5 to 0.7 mg/m <sup>2</sup> , IV, once)
25	Doxorubicin (25 mg/m <sup>2</sup> or 1 mg/kg, IV, once, as an infusion over 20 minutes)

\*Prednisone was continued at this dosage for the remainder of the treatment period.

If the cat was in remission at the end of week 9, treatment was continued at the beginning of week 11. If the cat was not in remission at the end of week 9 or had evidence of progressive disease earlier on during induction, an alternative rescue protocol was then used. If the cat was in remission at the end of week 25, treatment was continued at 3-week intervals, following the same sequence of drugs used in weeks 11 through 25, until week 51. If the cat was in remission at the end of week 51, treatment was continued at 4-week intervals, following the same sequence of drugs used in weeks 11 through 25, except that methotrexate was substituted for doxorubicin. Typically, cats with signs of progressive disease during the 2-, 3-, or 4-week treatment cycles returned to week 1 of the protocol for reinduction of remission.