Title

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Journal

Veterinary and comparative oncology, 14 Suppl 1(Suppl 1)

ISSN

1476-5810

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Publication Date

2016-08-01

DOI

10.1111/vco.12158

Peer reviewed

Published in final edited form as:

Vet Comp Oncol. 2016 August ; 14(Suppl 1): 136–146. doi:10.1111/vco.12158.

Treatment of feline intermediate to high-grade lymphoma with a modified university of Wisconsin–Madison protocol: 119 cases (2004–2012)

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Abstract

CHOP-based (cyclophosphamide, doxorubicin, vinca alkaloid, prednisolone) chemotherapy protocols are often recommended for treatment of feline lymphoma. While maintenance-free CHOP-based protocols have been published and readily used in dogs, there is limited literature regarding similar maintenance-free protocols in cats. The purpose of this study was to describe the outcome of cats with intermediate- to high-grade lymphoma that were prescribed a modified 25-week University of Wisconsin–Madison (UW-25) chemotherapy protocol. A secondary objective was examination of potential prognostic factors. One hundred and nineteen cats from five institutions treated with a UW-25-based protocol were included. The Kaplan–Meier median progression-free interval (PFI) and survival time (MST) were 56 and 97 (range 2–2019) days, respectively. Cats assessed as having a complete response (CR) to therapy had significantly longer

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*Correction added on 20 July 2016, after first online publication: The author, Dr. William Vernau, was previously omitted from the authorship of this article and has now been added in this current version.

Conflict of interest

None of the authors of this paper have financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

PFI and MST than those with partial or no response (PFI 205 versus 54 versus 21 days, respectively, P <0.0001 and MST 318 versus 85 versus 27 days, respectively, P <0.0001).

Keywords

cat; CHOP; feline; lymphoma; maintenance-free chemotherapy; survival

Introduction

Lymphoma is the most common haematopoietic neoplasmin the cat and accounts for approximately one third of all tumours in the cat. Prior to the 1990s, feline leukaemia virus (FeLV) was a major risk factor for the development of feline lymphoma and leukaemia. However, even with a decrease in the overall incidence of FeLV antigenemia over the past couple of decades, the incidence of feline lymphoma is still increasing, emphasizing the relevance of this disease in veterinary oncology.[1,2] Based on the National Cancer Institute's Working Formulation (WF) classification scheme, the majority of feline lymphomas have previously been identified as intermediate (35%) to high (50%) grade.[3] Factors reported to affect prognosis have included FeLV status, response to therapy, anatomic location, stage, grade, clinical substage and body weight.[4–13]

Numerous treatment protocols have been reported for feline lymphoma with varying results. The reported literature includes a wide variety of chemotherapy protocols, most commonly COP-based (cyclophosphamide, vincristine, prednisolone or prednisone) or CHOP-based (cyclophosphamide, doxorubicin, vinca alkaloid, prednisolone or prednisone) protocols that typically extend for a year or more. Importantly, these reports include various morphologic and anatomic forms of lymphoma ranging from high-grade alimentary lymphoma and renal lymphoma to types associated with longer survivals such as nasal lymphoma and small cell alimentary lymphoma.[14–17] Overall reported responses for feline lymphoma treated with various chemotherapy protocols range widely from 22 to 95%, with median survival times (MSTs) ranging from 50 to 388 days.[4–11,13,15,18–27]

Based on canine lymphoma studies that suggest lack of improved outcome with the addition of maintenance chemotherapy, some veterinarians began utilization of a similar CHOP-based, maintenance-free chemotherapy protocol for high-grade lymphoma in cats.[28–31] There is a paucity of studies examining the outcome in feline lymphoma patients receiving CHOP-based maintenance-free protocols, especially those without incorporation of non-CHOP drugs. The only study, known to the author, looking specifically at a short, maintenance-free, multi-agent, doxorubicin-containing protocol examined the efficacy and toxicity of the VELCAP-C protocol, which is a 24-week CHOP-based protocol. When compared with other studies, no improvement in survival (MST 62 days) was noted.[20]

Despite the increasing popularity of using a short protocol in cats, there is a paucity of data to support it. To date, there is little information on the outcome of cats with intermediate- to high-grade lymphoma treated with a maintenance-free chemotherapy protocol similar to the published University of Wisconsin, Madison (UWM)protocol for dogs. The purpose of this study was to describe the outcome of cats with intermediate- to high-grade lymphoma with

the intent to treat it with a UW-25-based chemotherapy protocol and to identify any potential prognostic factors for outcome.

Materials and methods

Medical records of cats examined at five institutions (University of California-Davis, University of Wisconsin–Madison, Auburn University, University of Illinois and Washington State University) between 2005 and 2012 for intermediate- or high-grade lymphoma were reviewed. Cats were included in the study if a diagnosis was confirmed by cytological or histological examination, a 25-week modified UWM protocol (see Table A1) was initiated and the medical record was complete. Prior use of prednisone or prednisolone was allowed. Cats having all gross disease removed surgically were allowed inclusion. Despite a known poor survival for cats with large granular lymphoma (LGL), those cases were still allowed inclusion because the diagnosis of LGL is difficult to make on histopathology and therefore could not be completely excluded. Cats were excluded if they had a diagnosis of small cell lymphoma, treatment intention was unclear, prior radiation or chemotherapy treatments had been performed or their chemotherapy protocol included significant modifications. Significant modifications that resulted in exclusion were substitution of any CHOP drugs with dissimilar drugs such as lomustine, methotrexate or chlorambucil. Information obtained from the medical record included age, breed, sex, results of FeLV and feline immunodeficiency virus (FIV) serologic tests as well as CBC (complete blood count), biochemical tests and available staging test results to aid in response determination, date of diagnosis, method of diagnosis, anatomic location of disease, response to treatment, date of progression, which vinca alkaloid was included, rescue therapies utilized, whether completion of the planned protocol was achieved, the number of doxorubicin doses given, date of death and cause of death. Data from institutions other than University of California, Davis (UCD) were collected via an online spreadsheet.

Polymerase chain reaction (PCR) assessment of antigen receptor gene rearrangement was performed using available archived tissue samples to determine immunophenotype on cases that were not immunophenotyped at diagnosis.

Anatomic location was classified as abdominal/alimentary (gastrointestinal, liver or diffuse abdominal lymph node involvement), mediastinal/intrathoracic, renal, multicentric (those with peripheral lymphadenopathy which may have also presented with the following: sternal node involvement, liver involvement or subcutaneous masses), or other (not fitting within the previously described categories). A subset of cats within the abdominal/alimentary group were defined as having LGL.

All cats were treated with a short 25-week modified UWM protocol (Table A1). Modifications allowed in the protocol included use of L-asparaginase at initiation of treatment (lengthening treatment by 1week to a 26-week protocol), vinblastine substitution for vincristine and the use of either prednisone or prednisolone at the discretion of the clinician. During each follow-up visit, physical exam findings and clinical signs were used to assess response along with diagnostic imaging tests (radiographs and/or ultrasound), if performed. Cats were classified as having a complete response (CR; regression of all

measurable disease and clinical signs), partial response (PR; decrease of >50% but <100% in the measurable disease) or no response (NR; decrease of <50% or an increase). No evidence of disease (NED) was used to describe response in cases that underwent surgery and no measurable disease was present at time of evaluation. Because this was a retrospective study, tumour measurements were not available in all patients for all visits. In some cases, determination of response was made in the clinician's notes. For cats with a palpable gastrointestinal tract mass without follow-up abdominal ultrasonography, CR was defined as a reduction in the size of the gastrointestinal 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 an increase or no change in size of the gastrointestinal tract mass. NED was reserved for cats that underwent surgery for diagnostic or therapeutic purposes with no disease detectable at the start of chemotherapy treatment (generally within 3 weeks of surgery) and at subsequent follow-up visits.

Statistical analyses

Endpoints evaluated were progression-free interval (PFI) and MST. PFI was defined as the time between diagnosis and the date that progression of disease was reported. Survival time was defined as the time between diagnosis and death as a result of lymphoma. Cats that died or were euthanized of unknown causes were presumed to be dead as a result of lymphoma. Cats alive without evidence of disease (NED or CR) lost to follow-up or dead from other causes were censored at the time of their last follow-up examination for calculation of overall MST. Cats alive with no evidence of lymphoma or dead without lymphoma (confirmed via necropsy) were censored for calculation of median PFI. The Kaplan–Meier product limit method was utilized to estimate PFI and MST.

Log-rank testing was utilized to compare outcome between groups. Variables assessed for their effect on survival and PFI included location, response to treatment (CR versus PR versus NR), vinca alkaloid used (vincristine versus vinblastine), immunophenotype, FeLV and FIV status, presence of anaemia (haematocrit >25% versus <25%), breed (Siamese versus all others), institution (UCD and UWM) and whether cytoreductive surgery was performed. Chi-squared testing was used to assess the effect of variables on response to therapy. Variables assessed included anatomic location, vinca alkaloid used (vincristine versus vinblastine), immunophenotype, FeLV and FIV status and presence of anaemia (haematocrit >25% versus <25%). A multivariate analysis was planned if significant associations based on univariate analysis were found. Statistical analyses were performed using commercial software (GraphPad Prism version 5.0c) and a P-value of <0.05 was considered significant.

Results

Patient characteristics

One hundred and nineteen cats met the criteria for inclusion in this study. Fifty each were from the UCD Veterinary Medical Teaching Hospital (VMTH) and the UWM VMTH. The remainder were from the University of Illinois (n=9), Auburn University (n=7) and Washington State University (n=3). A summary of the patient demographics is listed in

Table 1. The median age at diagnosis for all 119 cats was 11 years (range 1.3–19.1 years). Eight (6.7%) cats had surgery for diagnostic or therapeutic purposes that rendered them with immeasurable disease at the time of start of chemotherapy and thus response to chemotherapy (CR/PR/NR) could not be categorized. Seventy-five (63%) cats were classified as having an abdominal form, 19 (16%) were multicentric, 14 (11.8%) had mediastinal or intrathoracic lymphoma and 9 (7.6%) were classified as renal. Two (1.7%) cats were classified as other, one with spinal lymphoma and one with lymphoma of the tonsil and spleen. Of the cats presenting with the abdominal form, seven (6%) had LGL. One hundred and two cats (85.7%) had FeLV and FIV testing reported. Nine cats (9%) were positive for FeLV and four (4%) were positive for FIV. No cats were positive for both FeLV and FIV based on the available test results. Of the nine cats with FeLV positive status, all nine had mediastinal or intrathoracic involvement.

Ninety-six (81%) cats were diagnosed with cytology and 23 (19%) cats were diagnosed with histopathology. Immunophenotype was determined in 44 of the 119 cases. Twenty-four of the 96 cats that were diagnosed with cytology underwent immunophenotyping. Twenty-three were typed with PCR and one with immunocytochemistry. Of the 23 cats diagnosed with histopathology, only 20 had immunohistochemistry performed for immunophenotyping. Twenty-eight cats (63.6%) had B-cell lymphoma and 16 (36.4%) had T-cell lymphoma. Of the 29 cats with abdominal lymphoma that were immunophenotyped, 16 (55.2%) were B-cell and 13 (44.8%) were T-cell. Of the 15 remaining cats immunophenotyped that were not of the abdominal form, 8 were multicentric (seven B-cell, one T-cell), 4 were mediastinal/intrathoracic (three B-cell, one T-cell), 2 were renal (both B-cell) and one was spinal/other (T-cell).

Treatment response, prognostic factors and outcome data

For all 119 cats, median PFI was 56 days (range 2–2019; Fig. 1) and MST was 97 days (range 2–2019 days; Fig. 2). Eight cats were classified as having NED after surgical excision of their tumours. Forty-two (38%) of the remaining 111 cats with measurable disease experienced a CR, 27 (24%) achieved a PR and 42 (38%) were considered non-responders. Of the complete responders, 19 (45%) had abdominal lymphoma, 12 (29%) had the multicentric form, 6 (14%) had mediastinal/intrathoracic lymphoma, 4 (10%) had renal lymphoma and 1 (2%) was a spinal lymphoma (other). Ten of the 13 cats immunophenotyped that achieved a CR were B-cell while two of five cats achieving a PR were B-cell; 11 of 19 cats with NR were B-cell.

Eighty-five of the 119 (71.4%) cats died as a result of progression of their lymphoma. Twenty cats were lost to follow-up at times ranging from 28 to 1112 days (mean 531 days, median 145 days). Nine cats died of causes unrelated to their lymphoma confirmed on necropsy examination and eight of these cats were in CRs at the time of their death. The ninth cat was in a PR when he was hit by a car and killed. Of the eight cats in a CR at the time of death, cause of death included carcinoma (oral squamous cell carcinoma, pulmonary carcinoma and intestinal carcinoma), liver failure (unknown aetiology), acute bronchopneumonia, heart failure and renal failure. Two cats were alive with lymphoma (895

and 976 days from diagnosis) and three cats were alive in complete remission at the time of analysis (292, 914 and 1672 days from diagnosis).

Eighty-seven (73%) cats received at least one dose of doxorubicin (range 0–7, mean 1.68 doses) and 21 (18%) cats completed their prescribed CHOP protocol. Those cats that never received a dose of doxorubicin all had progression of disease and were either lost to follow-up or were euthanized prior to receiving doxorubicin. Five cats that had completed CHOP and were no longer receiving chemotherapy were restarted on CHOP when relapse occurred. One cat that had completed CHOP and was no longer receiving chemotherapy was restarted on COP at relapse as a result of renal insufficiency. The time between completion of CHOP chemotherapy and relapse, for these six cats, ranged from 23 to 379 days (mean 164 days, median 139 days).

Rescue therapy was utilized in 49 of 119 cats that were on CHOP therapy but had progression of their disease during treatment. Median number of rescues was one with 31 cats receiving one rescue therapy, 10 receiving two, 6 receiving three and 1 cat receiving four rescue therapies. Rescue therapies included L-asparaginase, lomustine (CCNU), chlorambucil (Leukeran®, Glaxo Smith Kline Research Triangle Park, NC, USA), cytarabine, mitoxantrone, vinblastine and mechlorethamine HCl. Three cats received radiation as a form of rescue therapy. Two received 6 Gy (one to the mediastinum and one to the mediastinum and larynx) and one cat received 8 Gy to the cranial abdomen.

PFIs and MST for cats responding (either CR or PR) to therapy were both significantly longer than those not responding to therapy ($P < 0.0001$). Median PFI for cats with CR was 205 days (range 13–1672) compared with 54 days (range 13–259) for those with PR and 21 days (range 2–85) for those with NR (Fig. 3). Patients achieving a CR had an MST of 318 days (range 13–1672) compared with 85 days (range 13–944) for PR and only 27 days (range 2–279) for NR (Fig. 4). Of the cats that achieved a CR, 43% were progression free at 1 year, 32% were progression free at 2 years and all 32% were progression free at 3 years.

Form was significant when evaluating PFI between those with LGL versus all other forms (27 versus 57 days, respectively; $P=0.01$) and MST between patients with renal lymphoma and all other forms (27 versus 105 days; $P=0.049$). When evaluating immunophenotype as a prognostic factor, no significance was shown for PFI or MST between B- and T-cell immunophenotype ($P=0.90$ and $P=0.30$, respectively). Even when examining the effect of immunophenotype within the group of cats with abdominal lymphoma, no significance was revealed for PFI or MST ($P=0.44$ and $P=0.10$, respectively). No other variables examined were predictive of PFI or MST. Results of the analyses are shown in Table 2. Anatomic location was also the only significant factor when evaluating variables in association with response to therapy. Cats with the alimentary form of lymphoma were less likely to achieve a CR than cats with all other anatomic locations combined. Only 30% of cats achieved CR in the alimentary group versus 52% in all other locations ($P=0.02$).

Discussion

There is currently no ‘gold standard’ for treatment of feline lymphoma and the result is a high variability in treatment regimens utilized amongst veterinarians. This study was performed to provide outcomes and prognostic information for one of the more commonly utilized chemotherapy protocols in the cat and, to date, it is the largest retrospective study evaluating a UW-25-based protocol for use in treatment of feline intermediate- to high-grade lymphoma, similar to that used as standard of care in dogs. It is also unique in that it specifically excludes cats with small cell gastrointestinal lymphoma, which typically have a better prognosis than cats with high-grade lymphoma. There is great variability in the grades, forms, stages and subtypes of lymphoma in cats. The low numbers of cats seen in clinical practice has often encouraged combining different anatomic forms and grades of lymphoma together in retrospective and prospective studies. This often makes interpretation of the data more challenging and the results potentially less clinically relevant. Another confounding factor for evaluating the current published literature is the inclusion of small cell (low grade) with high-grade lymphoma cases, either because the studies were performed at a time when the distinction was not made between histologic subtypes or because some cases of small cell lymphoma are treated with protocols that are typically reserved for higher grade lymphoma. Small cell lymphoma has historically been associated with a better prognosis than high-grade lymphoma which may have influenced outcome in prior reports that included cases with small cell lymphoma.[16,17,32,33]

Assessment of the published data is also challenging because feline lymphoma, as well as our ability to define and categorize it, has changed dynamically over the past few decades. Many of the earlier literature reports included high proportions of FeLV-infected cats, which has been shown to be associated with a poorer prognosis and also has significantly declined in prevalence since vaccination programmes were instituted in the 1980s.[5,7,8] This change has been accompanied by an ever increasing prevalence of the intestinal form of lymphoma in cats over the past three decades.[2] Although no distinction was made between histologic types in the studies in the immediate post-FeLV era, the alimentary form of lymphoma has historically accounted for the minority of cases, accounting for only 13–35% of the cases in studies published prior to 2005.[5–7,22,23,25,26] However, in studies published after 2005, there has been a steady increase in the intermediate- to high-grade alimentary form, and it now accounts for 42–57% of the feline lymphoma cases seen.[2,10,11,13,21] The study reported herein also has one of the highest reported percentages (63%) of the alimentary form of lymphoma, despite having excluded any small cell or low grade lymphoma cases. This is consistent with the temporal shift that has been observed in the post-FeLV era. This increase in the proportion of intermediate- to high-grade GI (gastrointestinal) lymphoma cases is of interest as more recent studies have also reported poor overall MSTs in cats treated for GI lymphoma, consistent with the results of the current study [2,6,10,11,13,21] Our study did show that the likelihood of achieving a CR was significantly lower in cats with the alimentary form when compared with the other forms. Possible explanations for this shift in survival times and lower response rate may be that the alimentary form is more chemo-resistant, or perhaps cats with intermediate to high-grade alimentary lymphoma are less likely to tolerate chemotherapy and may be euthanized sooner than those with other anatomic forms.

The response rates, PFI and MST reported here are comparable to other recent studies with similar patient characteristics.[10,11,20] Waite *et al.* reported a median PFI of 65.5 days and overall survival time of 108 days, which is comparable to the PFI of 56 day reported here. In a similar fashion, cats responding to treatment in both the Waite study and the study reported here also had significantly improved PFI and MST when compared with non-responders (PFI of 364 days and 205 days for CR, respectively; PFI of 31 and 21 days for NR, respectively; MST of 581 and 318 days for CR, respectively; MST of 73 and 27 days for NR, respectively). Another recent study by Krick *et al.* compared the use of vincristine versus vinblastine in a COP-based protocol for lymphoma in 40 client-owned cats. This study reported a progression-free survival of 48–64 days and a median lymphoma specific survival of 136–139 days, which is also comparable to the study reported herein.[11] Another study examined the use of VELCAP-C protocol, which is a more dose-intense 24-week CHOP-based protocol. Cats in that study had a CR rate of 43% and MST of 62 days which, again, is comparable to the 38% CR rate and MST of 97 days reported here.[20] In summary, the recent literature reports of feline lymphoma treated with CHOP-based protocols appear to have similarly poor response rates and overall survival times in comparison to older studies of feline lymphoma. Based on these data, there is a critical need to find new therapy options for cats with high-grade lymphoma.

Only a few of the factors examined were shown to be prognostic in this study. Response to therapy is one of the most consistent prognostic factors noted amongst the majority of feline lymphoma studies to date.[6,7,9,10,21] Similar to previous reports, cats that responded to therapy experienced significantly longer PFI and MST. Other studies have shown anatomic site to be prognostic as did our study, which revealed significantly different MST between the renal form compared with all other locations (MST 27 days versus 105 days, respectively; $P=0.0499$). The LGL subtype was also prognostic for PFI when compared with all other types (27 days versus 57 days, respectively; $P=0.01$). One limitation and a possible explanation for the lack of significance of other prognostic factors amongst the other anatomic forms is the low numbers of cases within these groups yielding low statistical power for analysis.

Approximately one third of cats were T-cell immunophenotype and two thirds were B-cell immunophenotype, which is a remarkably similar distribution of immunophenotype as seen in dogs. Interestingly, dogs with GI lymphoma are often of the T-cell immunophenotype, whereas the majority of cats with high-grade intestinal lymphoma in the study herein as well as the study conducted by Moore *et al.* had a fairly equal distribution of B- and T-cell immunophenotypes.[34] In contrast, cats with small cell lymphoma have been shown to be predominantly T-cell immunophenotype and have a much better outcome than cats with high-grade lymphoma.[16,17,35] A proposed reason for the lack of prognostic significance of immunophenotype on PFIs and survival times in previous studies was the inclusion of small cell and large cell lymphoma cases together in those analyses. However, in our study, immunophenotype was not found to be a significant prognostic factor for either PFI or MST (Table 2), even when comparing only the cases with the abdominal form of lymphoma.

In this study, 38% of cats achieved a CR when treated with the UW-25-based chemotherapy protocol. This number, while low, is similar to other reports of cats treated with various

protocols that include maintenance chemotherapy.[6,10,11,19–21,23,24] Our results also found that 43% of cats that achieved a CR remained disease-free at 1 year and, further, 32% of cats achieving a CR were disease-free at 2 and 3 years. Cats maintaining a CR at 2 years had no evidence of relapse by the end of the study. This finding indicates that long-term control or even cure is possible without maintenance chemotherapy in a subset of cats that experience a good response to treatment. Long-term maintenance chemotherapy can be associated with side effects including chronic hematologic toxicity, decreased appetite and weight loss, and these could be avoided in cats achieving a CR by using a maintenance-free protocol such as the one reported herein. With most cats in this study relapsing long before reaching the end of the 25-week protocol, the benefit of such a maintenance-free protocol is mainly to the subset of cats that achieve and sustain a CR. In that population, many cats sustain a prolonged remission without maintenance therapy.

Limitations in the study herein are similar to those inherent in a multi-institutional and retrospective study. Unlike dogs, there is no standard for staging for intermediate- to high-grade lymphoma in cats, and this leads to a limitation in the current study: a lack of standardized staging in cats with intermediate- to high-grade lymphoma. A commonly used World Health Organization (WHO) staging system is similar to the staging for dogs; however, such a system is not always applicable to cats as many cats do not fit clearly within a stage, prognosis has been inconsistently associated with clinical staging and cats are less likely to be completely staged (only nine cats in the current study were completely staged).[4,7,9,10,21,24,36] Definitions of the anatomic forms in cats are not standardized, and cats may not clearly fit into some categories, as it is common for cats to have disease that may overlap between forms. Another limitation of this study is the lack of consistent response criteria and restaging of cases to determine response. A number of cats with abdominal/alimentary lymphoma did not have regular follow-up ultrasounds to determine response; thus, in many cases clinical signs and physical exam notes in the medical record were used to determine the response. This made assessment of response somewhat subjective and may have underestimated or overestimated the number of responders as well as overall PFS. Staging is often influenced by cost to the client and clinician preference and cannot always be performed in a clinical setting. Another major limitation is the lack of standardized timing of staging and follow-up visits. The variability in timing of staging and follow-up and lack of consistency in monitoring is an inherent limitation of all retrospective studies. Additionally, most data in this study were extrapolated from the medical record notes or via contact with the referring veterinarian and/or owner, an additional limitation of a retrospective study. Another limitation is the lack of standardized rescue treatment. There were a large proportion of cats (41%) that went on to receive rescue therapies. This likely influenced overall survival in two ways: cats receiving rescue therapy may have survived longer than those not receiving rescue therapy and cats receiving rescue therapy may have been more likely to survive longer because their owners were willing to pursue additional therapy prior to considering euthanasia. While toxicity information would have been useful, collecting that data was difficult as a result of the large multi-institutional and retrospective nature of this study. Over half of the cases in this study had gastrointestinal involvement and thus commonly had symptoms such as weight loss, vomiting, decreased appetite or diarrhoea prior to initiation of treatment, making it difficult to elucidate if similar symptoms

during treatment could be attributed to treatment toxicity or disease. Thus, differentiating symptoms of disease from treatment toxicity was deemed too inconsistent to report in this retrospective multi-institutional study.

In summary, these data show that, overall, cats with intermediate to high-grade lymphoma have a poor prognosis. However, there is a population of cats within this group that may have long PFI and survival times. Response to treatment remains a consistent and important prognostic factor in cats with intermediate- to high-grade lymphoma, and this study did not identify any new predictors of survival. Interestingly, these data did show a significantly lower CR rate for cats with alimentary lymphoma when compared with all other forms. Future investigations should focus on identifying prognostic factors that can detect those cats that will respond favourably to chemotherapy, on discovery of new treatment modalities, and in identifying alternative protocols that should be utilized as first-line treatment in cats with high-grade lymphoma.

Acknowledgments

The authors thank the Center for Companion Animal Health (grant no. X04590) for providing funding for this study.

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Appendix

Table A1

Modified UW Madison (25 week) protocol

	Week																								
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**23**	**25**
L-asp[a]	x																							
Vinca[b]		x		x			x		x			x				x				x			x	
CTX[c]			x					x						x								x		
DOXO[d]					x					x								x						x
Pred[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[a] L-asparaginase was given at the discretion of the clinician at a dose of 400 IU kg^{-1} SQ or 2500 IU cat^{-1} SQ.

[b] Vincristine or vinblastine was given at the discretion of the prescribing clinician. Vincristine was given at 0.5–0.7mgm^{-2}, IV or vinblastine was given at 1.5mgm^{-2}, IV.

[c] Cyclophosphamide (Cytoxan) was given 200–250mgm^{-2} IV or PO.

[d] Doxorubicin was given at 1mg kg^{-1} or 25 mgm^{-2} IV.

[e] Prednisone or prednisolone was given at 1–2mg kg^{-1} PO q24 h continued through the protocol to be tapered upon completion. Tapering occurred earlier at the discretion of the clinician.

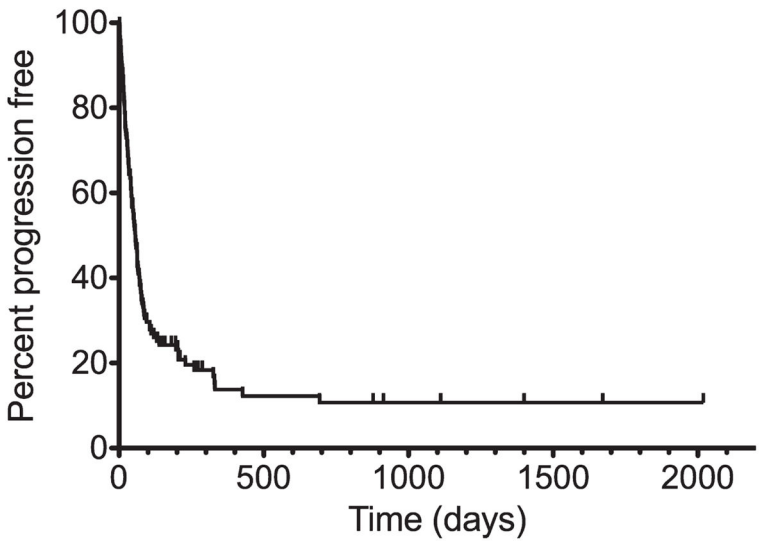

Figure 1.

Kaplan–Meier curve showing PFI of 119 cats with intermediate to high-grade lymphoma treated with a modified UW-25 protocol. Median PFI was 56 days.

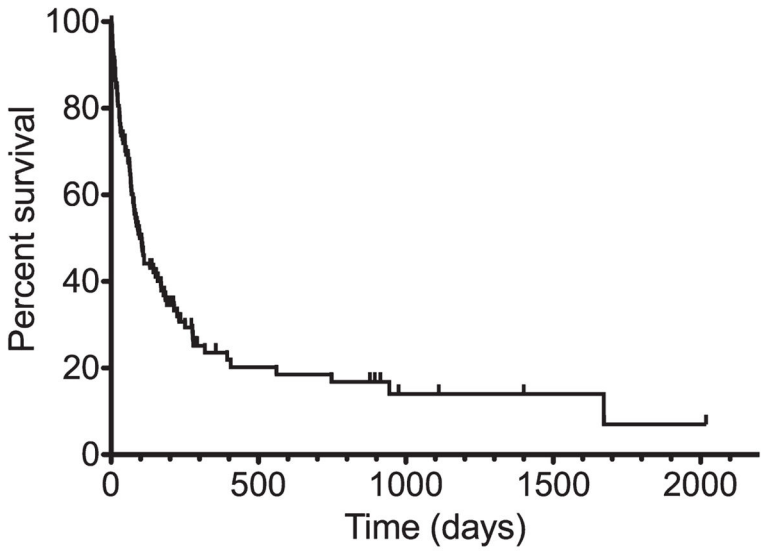

Figure 2.

Kaplan–Meier curve showing overall survival of 119 cats with intermediate-to high-grade lymphoma treated with a modified UW-25 protocol. Median survival time was 97 days.

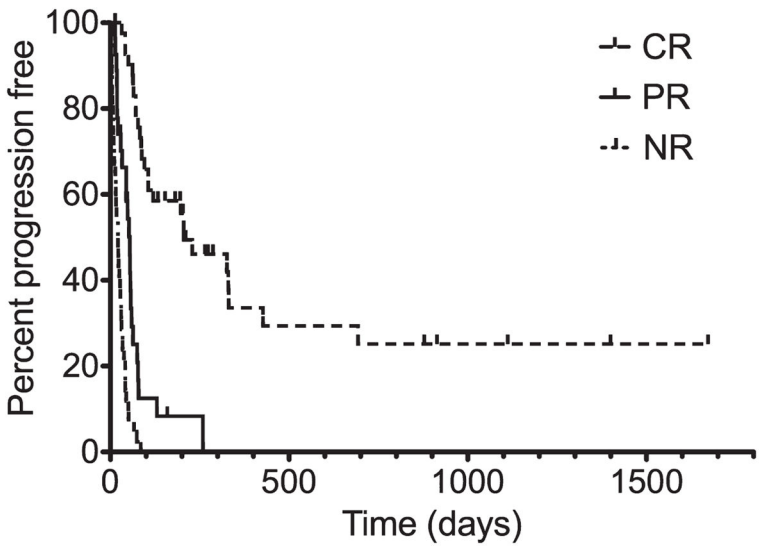

Figure 3.

Kaplan–Meier curve showing PFI of 119 cats with intermediate- to high-grade lymphoma stratified according to response to therapy. The median PFI for cats achieving a CR was 205 days, compared with 54 days for those achieving a PR and 21 days for those with NR to therapy.

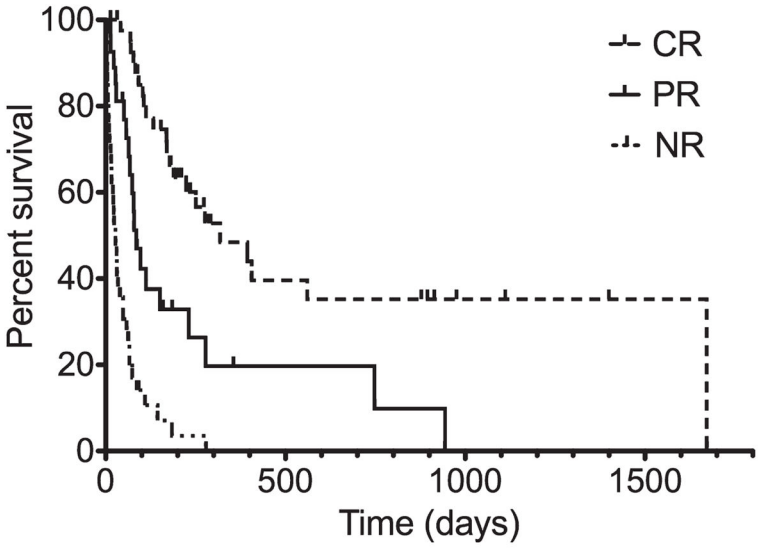

Figure 4.

Kaplan–Meier curve showing survival of 119 cats with intermediate- to high-grade lymphoma stratified according to response to therapy. The median survival time for cats achieving a CR was 318 days, compared with 85 days for those achieving a PR and 27 days for those with NR to therapy.

Table 1

Patient demographics

Variable	Category	*n* (of 119 cats)	%
Sex	Female intact	0	0
	Female spayed	54	45
	Male intact	1	0.8
	Male castrated	64	54
Breed	Domestic short hair	80	67
	Domestic medium hair	13	11
	Domestic long hair	12	10
	Maine coon	5	4
	Siamese	5	4
	Other	4	3
Anatomic location	Alimentary	75	63
	Multicentric	19	16
	Mediastinal/intrathoracic	14	12
	Renal	9	7.6
	Other	2	1.7
Immunophenotype	B-cell	28	63.6
	T-cell	16	36.4

Table 2

Results of analysis of factors predicting PFI and MST in feline intermediate- to high-grade lymphoma for all 119 cats

Variable	Median PFI	*P*-value	MST	*P*-value
Response to therapy		<0.0001		<0.0001
CR (*n*=42)	205		318	
PR (*n*=26)	54		85	
NR (*n*=42)	21		27	
Phenotype		0.90		0.30
B-cell (*n*=28)	55		144	
T-cell (*n*=16)	53		89	
Phenotype (abdominal only)		0.44	0.10	
B-cell (*n*=16)	50		144	
T-cell (*n*=13)	27		58	
Anatomic form		0.41		0.17
Abdominal (*n*=75)	50		85	
Multicentric (*n*=19)	74		189	
Mediastinal/intrathoracic (*n*=14)	64		82	
Renal (*n*=9)	23		27	
Anatomic form		0.11		0.0499
Renal (*n*=9)	23		27	
All others	56		105	
Anatomic form		0.72		0.59
Abdominal (*n*=75)	50		85	
All others	65		132	
Subtype		0.01		0.16
LGL (*n*=7)	27		105	
All others	57		31	
Anatomic form		0.07		0.18
Mediastinal (*n*=14)	33.5		74	
All others	59		105	
Institution		0.68		0.91
UC Davis (*n*=50)	57		112	
UW Madison (*n*=50)	52		92	
Vinca alkaloid		0.19		0.32
Vincristine (*n*=89)	51		103	
Vinblastine (*n*=27)	74		151	
Surgery		0.67		0.68
No surgery (*n*=114)	54		91	
Surgery performed (*n*=5)	63		158	
Anaemia		0.97		0.78
>25%	56		109	

Variable	Median PFI	*P*-value	MST	*P*-value
<25%	44		63	
FeLV status		0.89		0.58
Negative (*n*=93)	54		105	
Positive (*n*=9)	71		91	
FIV status		0.87		0.79
Negative (*n*=98)	55		97	
Positive (*n*=4)	85.5		122	
Breed		0.58		0.55
Siamese (*n*=5)	56		93	
Other	70		158	

[Correction added on 22 October 2015, after first online publication: The values under ‘Media PFI’ and ‘MST’ corresponding to Anatomic Form for Renal (*n*=9) and All Others were amended; the *n* value for Abdominal under Anatomic Form has been corrected to 75.]