Veterinary and Comparative Oncology

Original Article

DOI: 10.1111/vco.12243

A retrospective evaluation of lomustine (CeeNU) in 32 treatment naïve cats with intermediate to large cell gastrointestinal lymphoma (2006–2013)†

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Abstract

Multi-drug chemotherapy protocols for feline lymphoma have demonstrated variable efficacy and tolerability. In phase I trials, lomustine has demonstrated efficacy for cats with lymphoma though its use for treatment naïve feline intermediate/large cell gastrointestinal (GI) lymphoma remains unknown. This study evaluated the efficacy and tolerability of lomustine for the treatment of feline GI lymphoma. Thirty-two cats with histologically or cytologically confirmed intermediate/large cell GI lymphoma were evaluated retrospectively. Factors assessed included clinical signs, hematologic/biochemical parameters and use of L-asparaginase at induction. A response rate of 50% (16/32), with median duration of response of 302 days (range 64–1450 days), was found. Median progression-free interval was 132 days (range 31–1450 days), with overall median survival time of 108 days (range 4–1488 days). History of hyporexia, presence of anaemia and dose of lomustine were significantly associated with progression-free survival. Overall, lomustine is a well-tolerated and effective treatment for feline GI lymphoma.

Keywords
feline, gastrointestinal, lomustine, lymphoma

Introduction

Feline gastrointestinal (GI) lymphoma (LSA) is the most common form of lymphoma in the cat, comprising 27–72% of total cases in various reports.[1–5] Discrepancies in the incidence of primary GI LSA in these reports may be due to a decline in incidence of feline leukaemia (FeLV) associated non-GI forms of lymphoma as a result of the widespread availability of the FeLV vaccine and improved feline husbandry.[6]

GI LSA in the cat can arise within the stomach, small or large intestine and mesenteric lymph nodes. Cats may present with diffuse disease throughout the alimentary tract or with a focal lesion. Affected cats generally have a variable presentation with most experiencing one or all of the following: chronic weight loss, lethargy, inappetance, vomiting and diarrhoea (Leukeran tablets, GlaxoSmithKline, Research Triangle Park, NC).[1–5] Classically, cats are treated with multi-agent cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy protocols incorporating drugs such as vincristine (Vincristine powder for injection, Advacare Pharma, Wilmington, DE), cyclophosphamide (Cyclophosphamide injection, BDI Pharma, Columbia, SC), doxorubicin (Adriamycin for injection, Bedford Laboratories, Bedford, OH) and prednisone +/− L-asparaginase (Elspar, Merck & Co Inc, Whitehouse Station, NJ). An agreed

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†Preliminary results of this study were presented at the 28th Annual Conference of the Veterinary Cancer Society, October 19, 2008, Seattle, WA.

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upon 'standard of care' protocol, however, does not currently exist in the oncology community.[1–5,7–16] With a multi-agent treatment protocol, the prognosis for intermediate to large cell GI LSA is poor with a median survival time (MST) of 4–6 months. Response rates to chemotherapy average around 60–70%; however, only 11–54% achieve a complete response.[5–11,17] Indices for prognosis are limited in the cat; unlike the dog immunophenotype does not appear to carry prognostic significance in the cat.[4–6] To date, the most consistent positive prognostic indicator recognized throughout the veterinary literature for cats with GI LSA is a complete response to therapy.[1–5,7–16]

A number of retrospective studies have been completed that strive to better define an optimal treatment protocol for cats with GI LSA. Two studies exist evaluating the use of lomustine in cats with various types of neoplasia. Notably, 38–50% of feline lymphoma patients had an objective response to treatment.[18,19] Subsequent to these studies, a retrospective evaluation of lomustine as a rescue agent for 39 cats with chemotherapy resistant LSA was completed.[20] Results demonstrated that lomustine was well tolerated and provided an overall median progression-free interval (MPFI) for all cats of 39 days (7–708 days). One significant limitation to this study was the inclusion of cats with lymphoma of any grade (low, intermediate or high), any anatomic location and varying degrees of disseminated disease.[20] Nevertheless, results demonstrated biologic activity of lomustine in cats with primary GI LSA (MPFI 180 days) compared to cats with non-GI forms of lymphoma (MPFI 25 days). These results support the use of lomustine in the treatment of GI LSA in cats.[20]

Lomustine (CeeNU (Lomustine) capsules, Bristol-Myers Squibb Co., Princeton, NJ) (CeeNU) is classified as an anti-tumour alkylating agent in the nitrosourea family.[21] The nitrosoureas are highly lipid soluble, with rapid transport across the blood–brain barrier.[21,22] In humans, lomustine has been shown to be effective in the treatment of refractory Hodgkin's lymphoma and in the treatment of primary and metastatic brain tumours.[22,23] In the dog, lomustine has been reported to be a useful rescue agent for multi-centric LSA.[24,25] Lomustine has also been shown to possess activity against canine mast cell tumours and cutaneous manifestation of LSA.[26]

Currently, a paucity of information exists regarding the safety and efficacy of lomustine in cats, although it has been used to treat cats with LSA, fibrosarcoma, multiple myeloma, hepatocellular carcinoma, squamous cell carcinoma and various other neoplasias.[18] Toxicoses associated with lomustine administration in cats, such as leukopenia, thrombocytopenia, and sepsis, have been reported.[18] Likewise, there is little information on the optimal dosage of lomustine in cats. One study suggests a dosage of 50–60 mg m^{-2} every 6 weeks is optimal.[18,19] Another study reports that a standard dosing of a 10 mg capsule regardless of body size to be well tolerated and effective.[19]

The purpose of this retrospective study was to evaluate the response rate and survival time for cats with intermediate to large cell GI LSA treated with lomustine as first-line therapy. Our secondary objective was to document hematologic toxicities secondary to lomustine administration in treatment naïve cats with GI LSA. To our knowledge, there are no prior reports in the veterinary literature evaluating the efficacy of lomustine as a first-line treatment of feline intermediate to large cell GI LSA.

Methods and materials

Case selection

Medical records of cats evaluated at the Harrington Oncology Program at Tufts Cummings School of Veterinary Medicine in North Grafton, MA, Carolina Veterinary Specialists in Greensboro, NC, and Metropolitan Veterinary Associates in Norristown, PA, between 2006 and 2013 for GI lymphoma were reviewed retrospectively. Cytologic classification of large/intermediate cell versus small cell lymphoma was based on lymphocyte size as compared to an associated normal neutrophil (10 μM). Cats were included in the study if they had a cytologically or histologically confirmed diagnosis of intermediate to large cell (defined as lymphocytes >15 μM) GI LSA along with changes on imaging of the GI tract consistent with lymphoma involvement (visible mass, wall thickening and/or loss of wall layering) and there was intent to treat with a lomustine as first-line therapy.

Data collection

Patient variables

Data collected included the following: clinical signs at the time of diagnosis, physical examination findings, hematologic data, FeLV and feline immunodeficiency virus (FIV) testing, thoracic radiography, abdominal ultrasound, methods used to confirm diagnosis of lymphoma and immunophenotyping results.

Treatment and outcome

Data collected from the medical records included chemotherapy drugs administered, frequency of chemotherapy administration, response to treatment, duration of response, survival times and adverse events when noted in the medical record. The dose of lomustine administered varied considerably with most clinicians starting at approximately 40 mg m^{-2} (range 30–60 mg m^{-2}). Some patients received a single dose of L-asparaginase with the first lomustine treatment or that had concurrent steroid administration were included. Cats receiving L-asparaginase were included in this study based on a study completed by LeBlanc et al. in which the addition of L-asparaginase provided minimal benefit to cats with GI LSA.[27] It was recommended that complete blood cell count (CBCs) be monitored weekly during the first cycle of lomustine. Cats were treated every 4–6 weeks, depending on the neutrophil nadir of each individual. A CBC was also performed prior to each treatment and lomustine was administered if the neutrophil count was 3000 μL^{-1} or greater and platelet count was 100 000 μL^{-1} or greater on the day of treatment. The total number of lomustine treatments varied depending on the tolerance of each individual's bone marrow and duration of disease response. Biochemistry profiles were not regularly completed or routinely noted in the medical record, therefore assessment for alterations in liver enzymology was not done.

Response assessment

Cats were evaluated for response to treatment both subjectively via abdominal palpation and clinical signs and objectively with periodic ultrasonography.

When an abdominal ultrasound was repeated, the following criteria were used to evaluate the response to treatment: complete remission (CR), 100% reduction in size of all measurable disease; partial remission (PR), >50% but <100% reduction in size of all measurable disease; stable disease (SD), <50% reduction in size of all measurable disease, no change in size, or <25% increase in size of overall measurable disease; progressive disease (PD), >25% increase in size of overall measurable disease or the appearance of new lesions.

For cats in which an abdominal ultrasound was not repeated, subjective criteria (abdominal palpation and estimate of mass size) along with the resolution of clinical signs were used to assess a patient's response. The resolution of a mass via palpation alone was classified as a PR, so as not to overestimate the number of CRs.

All responses were required to last for a minimum of 28 days (4 weeks) since this was the minimum-dosing interval between treatments for patients receiving lomustine. Shorter responses would not be clinically relevant, as patients would be unable to continue the protocol.

Toxicity assessment

Toxicosis was defined as an adverse event that was severe enough to warrant a reduction in dose of any chemotherapy agent. All toxicoses were graded according to the VCOG-CTCAE.[28] Due to the retrospective nature of this study, GI toxicoses that did not necessitate a dose reduction or delay in treatment were inconsistently reported and therefore not evaluated.

Statistical analysis

Response rate was defined as the number of cats achieving a CR or PR compared to the total number of cats treated. Duration of response, progression-free interval (PFI) and MST were determined using the Kaplan–Meier product limit analysis and were calculated from the first day of chemotherapy treatment. Endpoints for the study were tumour progression and patient death. For the duration of response and PFI, patients whose tumours had not progressed were censored at the date of their last visit. For MST, patients who

were alive, died from another cause or were lost to follow-up were censored at the date of their last visit.

Both the duration of response and PFI were calculated in this study. For some cats with GI LSA, stabilization of measurable disease may still result in resolution of clinical signs and improvement in quality of life and therefore continuation of treatment. As a result, it was considered relevant to report, not just those cats achieving complete or partial responses (duration of response), but also those cats achieving SD (PFI).

The following variables were evaluated for significance on the duration of response, PFI and MST using the Mann–Whitney *U* test: age, gender, viral status, anaemia at presentation, prior history of hyporexia, prior history of weight loss, use of L-asparaginase at the start of the protocol, dose of lomustine administered and debulking surgery prior to chemotherapy. Factors with a *P* value <0.05 were considered significant. Factors identified as significant with univariate analysis were then placed into multivariate analysis using Cox regression with all factors found to have a *P* value <0.1 on univariate testing. Again, factors with a *P* value <0.05 were considered significant. All statistical analyses were performed with a statistical software program (StatsDirect Statistical Software, StatsDirect Ltd, Cheshire, Wales, UK).

Results

Patient population

Records from 32 cats with intermediate to large cell GI lymphoma with the intent to treat with lomustine chemotherapy were identified and reviewed. The characteristics of these patients, including signalment and presenting clinical signs, are summarized in Table 1.

Four patients had a debulking surgery performed prior to initiation of the lomustine protocol. Although the intestinal lesion was resected in these four cats, additional ultrasonographic abnormalities (lymphadenopathy, hepatomegaly and/or abdominal effusion) were present and used to measure response to therapy.

No cats had received chemotherapy or steroids prior to initiating lomustine. Patients were treated with lomustine at a starting dose of 30–60 mg m^{-2} (median 40 mg m^{-2}). In 31 cats, this corresponded to a dose of one 10 mg capsule per cat. The largest cat in the study (7.5 kg) received a starting dose of 20 mg, which was still within the 30–60 mg m^{-2} dose range (52 mg m^{-2}). All but four patients (87.5%) received concurrent steroid therapy in conjunction with lomustine. Of these, 28 cats receiving steroids, 27 were started on prednisolone or prednisone at a dose of 2 mg kg^{-1} orally daily. One cat was given monthly injections of depomedrol due to the owner's inability to administer oral

Table 1. Signalment, presenting complaint and staging information for cats with intermediate to large cell gastrointestinal lymphoma receiving lomustine

	Lomustine
Age-median (years)	11 (3–16)
Sex	
MI	1/32 (3%)
MC	15/32 (47%)
FI	0/32 (0%)
FS	16/32 (50%)
Clinical signs at presentation	
Hyporexia	23/32 (72%)
Weight loss	18/32 (56%)
Vomiting	16/32 (50%)
Lethargy	13/32 (41%)
Diarrhoea	4/32 (13%)
Complete blood count	
Anaemia (Hct <30%)	16/32 (50%)
Mature neutrophilia (Neuts >13 000 μL^{-1})	9/32 (28%)
Chemistry profile	
Azotemia	3/32 (9%)
Elevated liver values	4/32 (13%)
Hypoalbuminemia	5/32 (16%)
Urinalysis	
Isosthenuria	4/18 (22%)
Viral status	
FeLV	1/15 (7%)
FIV	0/15 (0%)
Chest radiographs	
Mediastinal mass	3/17 (18%)
Pleural effusion	1/17 (6%)
Lymphadenopathy	1/17 (6%)
Abdominal ultrasound	
GI thickening w/altered layering or mass	29/31 (94%)
Lymphadenopathy	24/31 (77%)
Abdominal effusion	7/31 (23%)
Renomegaly	3/31 (10%)
Splenomegaly	3/31 (10%)
Hepatomegaly	2/31 (6%)

MI, Male intact
MC, Male castrated
FI, Female intact
FS, Female spayed
Hct, Hematocrit

medications. Fourteen patients (44%) received a single treatment of L-asparaginase at a dose of 10 000 units M^{-2} subcutaneously simultaneously with the first lomustine chemotherapy.

Diagnosis and clinical staging

A diagnosis of intermediate to large cell lymphoma was made by biopsy of a lymph node or GI mass in 11 cats, and by fine needle aspirate in the remaining 21 cats.

Results of staging tests performed are summarized in Table 1. All 32 cats had a pre-treatment CBC and serum biochemistry profile available for evaluation. Eighteen of 32 cats had a urinalysis performed. Viral status was available for 15 cats. Chest radiographs were performed in 17 of 32 cats. Thirty-one patients had an abdominal ultrasound performed prior to treatment with the lomustine protocol. The remaining cat had an abdominal exploratory in which the palpable intestinal mass and associated lymph nodes were biopsied, but not removed. Response assessment for this cat was based on the measurements obtained via abdominal palpation both prior to and after starting treatment.

Adverse events

Twenty-five of the 32 cats had weekly complete blood counts performed and available for review after the first lomustine chemotherapy treatment. Neutropenia occurred secondary to lomustine administration in 13 of the 25 cats (52%). In these cats, neutropenia was classified as grade 1 ($n = 2$), grade 2 ($n = 3$), grade 3 ($n = 6$) or grade 4 ($n = 2$). None of the neutropenic events experienced by these cats required hospitalization nor resulted in sepsis. The median time to neutrophil nadir after receiving lomustine was 3 weeks (range 1 – 5 weeks).

Two cats required a lomustine dose reduction due to grade 4 neutropenia. Both patients were initially treated with 10 mg of lomustine. Each received a 25% dose reduction, and was subsequently treated with 7.5 mg lomustine (compounded). The first patient received 43 mg M^{-2} at the initial dose, which was reduced to 33 mg m^{-2} after the dose reduction. The second patient received 30 mg m^{-2} at the initial dose, which was reduced to 23 mg m^{-2} after the dose reduction. These dose reductions were deemed adequate via blood work performed subsequent to the administration of the 7.5 mg dose of lomustine.

No GI-related toxicities requiring dose reductions or delays were noted in any patients during the course of lomustine treatment. Cats receiving concomitant L-asparaginase with lomustine at induction chemotherapy did not have increased frequency of toxicity.

Table 2. Response, remission and survival information for cats with intermediate to large cell gastrointestinal lymphoma receiving lomustine

	Lomustine
Response	
CR	7 (22%)
PR	9 (28%)
SD	5 (16%)
PD	11 (34%)
Median duration of response (days)	302 (64 – 1450)
Median progression-free interval (days)	132 (31 – 1450)
Median survival time (days)	
Overall (CR + PR + SD + PD)	108 (4 – 1488)
Responders and stable (CR + PR + SD)	215 (53 – 1488)
Responders (CR + PR)	330 (84 – 1488)

Outcome

Response, remission and survival data are summarized in Table 2. Seventeen cats were evaluated objectively for response using a repeat abdominal ultrasound. Fifteen cats were subjectively assessed for response relying on abdominal palpation of masses. Of the 32 patients started on the lomustine protocol, responses were as follows: CR: 7 (22%), PR: 9 (28%), SD: 5 (16%), PD: 11 (34%). The overall response rate (CR + PR) was 50%, with a median duration of response of 302 days (range 64 – 1450 days).

For the 66% of patients experiencing a CR, PR or SD in response to lomustine, the MPFI was 132 days (range 31 – 1450 days). The MST for all 32 cats treated with lomustine was 108 days (range 4 – 1488 days, Fig. 1). Six cats were censored during survival analysis. Two patients were still alive and in remission. One of these cats was in a PR at 88 days and the other was in a CR at 1276 days. One cat was alive and in a PR at 213 days, but was subsequently lost to follow-up. Two patients died of causes other

than lymphoma while in PR at 94 and 96 days, one from renal failure and the other from pure red blood cell aplasia attributed to darbepoetin therapy. One patient was still alive at 140 days, though had recently progressed while on lomustine.

Factors associated with shorter median response duration (MRD), PFI or MST on both univariate and multivariate analysis included presence of hyporexia at presentation, anaemia (packed cell volume <30%) and the dose of CeeNU administered (<40 mg m^{-2}). Hyporexic cats ($n = 23$) had a PFI of 94 versus 362 days for non-anorexic cats ($n = 9$) ($P = 0.0193$). Cats presenting with an anaemia of <30% ($n = 16$) had a reduced MRD, PFI and MST compared with non-anaemic cats ($n = 16$). Anaemic cats had an MRD of 95 days, PFI of 57 days and MST of 67 days compared to non-anaemic cats with an MRD of 322 days ($P = 0.0097$), PFI of 140 days ($P = 0.0138$) and MST of 128 days ($P = 0.0205$). Cats receiving lomustine at >40 mg M^{-2} had a longer PFI of 213 days versus 75 days for cats receiving <40 mg m^{-2} ($P = 0.0127$).

Age, presence of documented weight loss, prior surgery, treatment with L-asparaginase at induction and diagnosis of large granular lymphocyte (LGL) were not statistically significant for MRD, PFI or MST in this population of cats.

The median number of lomustine treatments was three (range 1–11), with a median interval between lomustine treatments of 5 weeks (range 4–7.5 weeks). Three cats were in a CR after receiving more than six treatments, at which point the attending clinician elected to stop therapy. One cat that received eight lomustine treatments remains in a CR at 1276 days. A second cat that received seven treatments with lomustine was in a CR for 1450 days before disease progression was noted. Further, chemotherapy was not pursued and the patient died at 1488 days. The third also received seven lomustine treatments and was in a CR until it experienced disease progression in the small intestines at 362 days, at which time lomustine was restarted. This patient achieved a second CR lasting 155 days, and subsequently was rescued with cyclophosphamide due to PD.

Four patients were still receiving lomustine and in a remission at their censoring date (88, 94, 96 and 213 days). The remaining 25 patients failed to complete the planned lomustine course due to disease progression. Fourteen cats did not receive additional therapy, while 11 of the cats received some form of rescue chemotherapy. One patient with lymphoma seeding to the abdominal wall received palliative radiation therapy, and had a PR lasting 66 days. Seven cats received rescue chemotherapy consisting of CHOP-based drugs. Two of these patients experienced PRs lasting 85 and 94 days, while the remaining five experienced PD. Two cats were treated with L-asparaginase alone, and had PD. The final cat was rescued with bleomycin, and failed to respond.

Of the 32 cats with intermediate to large cell GI lymphoma in this study, 9 had features on pathology that classified them as LGL lymphoma. Responses to lomustine for the LGL lymphoma cats were as follows: CR: 3 (33.3%), PR: 2 (22.2%), SD: 1 (11.1%), PD: 3 (33.3%). The overall response rate (CR + PR) was 55.6%, with an MRD of 140 days (range 96–362 days). For the 66.6% patients with LGL GI lymphoma having a CR, PR or SD in response to lomustine, the median PFI was 140 days (range 48–362 days). The MST for the nine cats with LGL lymphoma treated with lomustine was 129 days (range 8–576 days). There was no statistical significant difference in MRD ($P = 0.807$), PFI ($P \geq 0.999$) and MST ($P = 0.5042$) between cats with a diagnosis of LGL GI LSA as compared to cats without features of LGL.

Discussion

The purpose of this retrospective study was to evaluate the response rate and survival time for cats with intermediate to large cell GI lymphoma treated with lomustine as first-line therapy. Results of this study revealed that a lomustine protocol yielded an overall response rate (CR + PR) of 50%, with a median duration of response of 302 days (range 64–1450 days). This response rate is similar to previously reported response rates ranging from 18 to 63% for feline large cell GI lymphoma treated with various continuous and discontinuous multi-agent protocols.[4,5,7–16] The association of hyporexia and anaemia at presentation with poor response duration or PFI has been previously demonstrated in both cats and dogs diagnosed with LSA and may

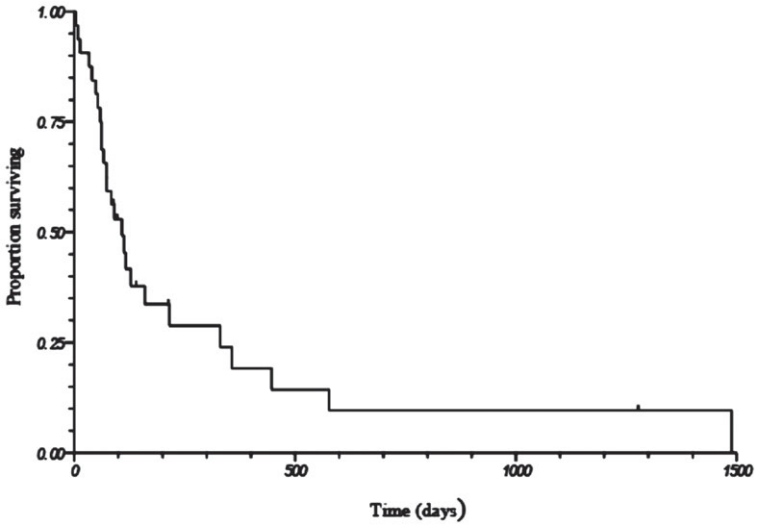

Figure 1. Kaplan–Meier curve depicting survival time (in days) for cats with intermediate to large cell gastrointestinal lymphoma treated with a lomustine chemotherapy protocol. Vertical bars represent cats censored analysis.

reflect the presence of more advanced or aggressive disease.[5,29,31] Consequently, cats presenting with these clinical findings should be considered to have a worse prognosis.

Another prognostic factor associated with PFI included cats receiving lomustine at a dose of 40 mg m^{-2} or greater. While the ideal dosing of lomustine in cats has not been established, based on these results, clinicians should strive to administer a dose that is on the higher end of a range.

For this study, we elected to include cats that received a single injection of L-asparaginase given past studies indicating no significant benefit in response or survival for this drug when used in cats with GI LSA.[27] Similar to what has been reported in the dog with multi-centric LSA, a combination of L-asparaginase with CCNU in 14 cats with GI LSA appeared to be well tolerated but provided no significant improvement in MRD, PFI or MST in this study.

Overall, the protocol was well tolerated. Although neutropenia was a common sequela during the protocol, most episodes were not clinically significant. GI toxicoses requiring dose delay or dose adjustment were not reported.

The most common reasons for owners to elect lomustine as primary treatment included the decreased cost and ease of administration. Results of this study suggest that lomustine may be a reasonable alternative to multi-agent protocols, especially in situations where an owner has financial constraints or a patient does not tolerate weekly chemotherapy treatments.

In this study, when evaluating a patient's response to treatment, both the duration of response and PFI was calculated. For some cats with GI LSA, stabilization of measurable disease may be a reasonable treatment outcome if these cats still have improvement in their quality of life with the resolution of clinical signs such as inappetance, vomiting, diarrhoea and weight loss. Therefore, it appeared relevant to report not only cats achieving complete and partial responses but also those maintaining disease stabilization. The progression-free rate (CR + PR + SD) was 66%, with a MPFI of 132 days (range 31–1450 days).

The MST for all 32 cats treated with lomustine was 108 days (range 4–1488 days). While direct comparisons cannot be made, this MST is situated within the shorter end of the range reported in previous studies of 2–10 months.[5,10,11] There are several potential reasons for this relatively shorter survival time relative to the similar response rate seen in previous studies evaluating multi-agent protocols. One possibility is that a multi-agent chemotherapy regimen may be more effective at maintaining a durable remission for feline intermediate to large cell GI lymphoma compared to single

agent lomustine. It is also possible that clinicians may have been more inclined to recommend a chemotherapy regimen such as lomustine, which is perceived as being better tolerated, when a cat was exhibiting more severe GI signs at presentation. This bias could have resulted in an increased population of cats presenting with more severe constitutional signs related to the LSA. Approximately 70% of cats included in this study presented with signs of hyporexia and weight loss. Additionally, many cats in this study received lomustine because their owners had already declined other more intensive chemotherapy regimens such as a CHOP-based protocol. It is possible that the patient population was therefore biased with animals whose owners were not interested in pursuing rescue therapies when a cat either failed to respond or came out of remission.

In a previous report, cats with LGL lymphoma receiving various combinations of treatment experienced a response rate of 30.4% (7/23) with an overall MST of 57 days.[30] In this study, the subset of cats with LGL lymphoma treated with lomustine +/− L-asparaginase had an overall response rate of 55.6% (5/9), with an MRD of 140 days (range 96–362 days). The overall MST in this population was 129 days (range 8–576 days). Although the sample size is low, this more favourable response rate and survival time for LGL lymphoma cats receiving lomustine treatment warrants further evaluation in future studies.

Limitations of this study include its retrospective nature. As a retrospective study, objective response criteria were not available for all patients evaluated. As well treatment was not standardized for dose of lomustine administered and there was a proportion of cats that received the addition of L-asparaginase at the start of their treatment regimen. Additionally, a single pathologist did not review all cytology or histopathology samples and biopsies were not obtained on all patients. Distinguishing inflammatory bowel disease from intestinal lymphomas in cats can be challenging especially with cytologic or superficial endoscopic biopsy samples. The addition of immunohistochemistry and polymerase chain reaction clonality assay may improve diagnostic accuracy.

The inclusion of cats diagnosed with an LGL form of lymphoma may be viewed as a limitation given this diagnosis is considered to be far more aggressive than intermediate to large cell lymphoma. However, we elected to include this population of cats as this form of lymphoma remains an enigma in veterinary medicine with limited studies evaluating effective therapies.[30] Because past studies have demonstrated a significantly worse prognosis for cats with LGL forms of lymphoma, it was reasoned that including these patients in our study would not result in an artificial increase in PFI or MST therefore should not overstate our results. Instead, including this population of cats may result in an understatement of the success of this treatment. However, based on the data in this study, it appears this concern is not warranted given the lack of statistical significance between the two populations. Based on this and the relatively unclear behaviour of LGL lymphoma, the authors concluded the positive response achieved with lomustine was notable and worth reporting. This component of the study is compelling and as mentioned above supports the need for prospective or larger retrospective studies evaluating cats with intestinal LGL forms of lymphoma treated with lomustine as a first-line therapy.

Overall, results of this study conclude that lomustine is well tolerated and can be used as an effective treatment for intermediate to large cell GI LSA in cats.

References

1. Milner RJ, Peyton J, Cooke K, Fox LE, Gallagher A, Gordon P, *et al.* Response rates and survival times for cats with lymphoma treated with the University of Wisconsin-Madison chemotherapy protocol: 38 cases (1996-2003). *Journal of the American Veterinary Medical Association* 2005; **227**: 1118–1122.
2. Hadden AG, Cotter SM, Rand W, Moore AS, Davis RM and Morrissey P. Efficacy and toxicosis of VELCAP-C treatment of lymphoma in cats. *Journal of Veterinary Internal Medicine* 2008; **22**: 153–157.
3. Kristal O, Lana SE, Ogilvie GK, Rand WM, Cotter SM and Moore AS. Single agent chemotherapy with doxorubicin for feline lymphoma: a retrospective study of 19 cases (1994-1997). *Journal of Veterinary Internal Medicine* 2001; **15**: 125–130.

4. Mooney SC, Hayes AA, Matus RE, MacEwen EG, Matus RE, Geary A, *et al.* Treatment and prognostic factors in lymphoma in cats: 103 cases (1977-1981). *Journal of the American Veterinary Medical Association* 1989; **194**: 696–699.
5. Waite AHK, Jackson K, Grego TP and Krick EL. Lymphoma in cats treated with weekly cyclophosphamide, vincristine and prednisone protocol: 114 cases (1998-2008). *Journal of the American Veterinary Medical Association* 2013; **242**: 1104–1109.
6. Louwerens M, London CA, Pedersen NC and Lyon LA. Feline lymphoma in the post-feline leukaemia virus era. *Journal of Veterinary Internal Medicine* 2005; **19**: 329–335.
7. Zwahlen CH, Lucroy MD, Kraegel SA and Madewell BR. Results of chemotherapy for cats with alimentary lymphoma: 21 cases (1993-1997). *Journal of the American Veterinary Medical Association* 1998; **213**: 1144–1149.
8. Mahoney OM, Moore AS, Cotter SM, Engler SJ, Brown D and Penninck DG. Alimentary lymphoma in cats: 28 cases (1988-1993). *Journal of the American Veterinary Medical Association* 1995; **207**: 1593–1597.
9. Fondacaro JV, Richter KP, Carpenter JL, Hart JR, Hill SL and Fettman MJ. Feline gastrointestinal lymphoma: 67 cases (1988–1996). *European Journal of Comparative Gastroenterology* 1999; **4**: 5–11.
10. Simon D, Eberle N, Laacke-Singer L and Nolte I. Combination chemotherapy in feline lymphoma: treatment outcome, tolerability, and duration in 23 cats. *Journal of Veterinary Internal Medicine* 2008; **22**: 394–400.
11. Teske E, van Straten G, van Noort R and Rutteman GR. Chemotherapy with cyclophosphamide, vincristine, and prednisolone (COP) in cats with malignant lymphoma: new results with an old protocol. *Journal of Veterinary Internal Medicine* 2002; **16**: 179–186.
12. Vail DM, Moore AS, Ogilvie GK and Volk LM. Feline lymphoma (145 cases): proliferation indices, cluster of differentiation 3 immunoreactivity, and their association with prognosis in 90 cats. *Journal of Veterinary Internal Medicine* 1998; **12**: 349–354.
13. Cotter SM. Treatment of lymphoma and leukemia with cyclophosphamide, vincristine, and prednisone: II. Treatment of cats. *Journal of the American Animal Hospital Association* 1983; **19**: 166–172.
14. Jeglum KA, Whereat A and Young K. Chemotherapy of lymphoma in 75 cats. *Journal of the American Veterinary Medical Association* 1987; **190**: 174–178.
15. Malik R, Gabor LJ, Foster SF, McCorkell BE and Canfield PJ. Therapy of Australian cats with lymphosarcoma. *Australian Veterinary Journal* 2001; **79**: 808–817.
16. Moore AS, Cotter SM, Frimberger AE, Wood CA, Rand WM and L'Heureux DA. A comparison of doxorubicin and COP for maintenance of remission in cats with lymphoma. *Journal of Veterinary Internal Medicine* 1996; **10**: 372–375.
17. Stein TJ, Pellin M, Steinberg H and Chun R. Treatment of feline gastrointestinal small cell lymphoma with chlorambucil and glucocorticoids. *Journal of the American Animal Hospital Association* 2010; **46**: 413–417.
18. Rassnick KM, Gieger TL, Williams LE, Ruslander DM, Northrup NC, Kristal O, *et al.* Phase I evaluation of CCNU (lomustine) in tumor-bearing cats. *Journal of Veterinary Internal Medicine* 2001; **15**: 196–199.
19. Fan TM, Kitchell BE, Dhaliwal RS, Jones PD, Hintermerister JG and Paria BC. Hematological toxicity and therapeutic efficacy of lomustine in 20 tumor-bearing cats: critical assessment of a practical dosing regimen. *Journal of the American Animal Hospital Association* 2002; **38**: 357–363.
20. Dutelle AL, Bulman-Fleming JC, Lewis CA and Rosenberg MP. Evaluation of lomustine as a rescue agent for cats with resistant lymphoma. *Journal of Feline Medicine and Surgery* 2012; **14**: 694–700.
21. Chabner BA and Longo DL. *Cancer Chemotherapy and Biotherapy Principles and Practice*. 4th edn., Philadelphia, Lippincott Williams and Wilkins, 2006.
22. Finlay JL, Boyett JM, Yates AJ, Wisoff JH, Milstein JM, Geyer JR, *et al.* Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine and prednisone with the eight drugs in 1 day regimen. *Journal of Clinical Oncology* 1995; **13**: 112–123.
23. Williams SD and Einhorn LH. Combination chemotherapy with doxorubicin and lomustine. Treatment of refractory Hodgkin's disease. *Journal of the American Medical Association* 1977; **238**: 1659–1661.
24. Moore AS, London CS, Wood CA, Williams LE, Cotter SM, L'Heureux DA, *et al.* Lomustine (CCNU) for the treatment of resistant lymphoma in dogs. *Journal of Veterinary Internal Medicine* 1999; **13**: 395–398.
25. Saba CF, Hafeman SD, Vail DM and Thamm DH. Combination chemotherapy with continuous L-asparaginase, lomustine and prednisone for relapsed canine lymphoma. *Journal of Veterinary Internal Medicine* 2009; **23**: 1058–1063.

26. Risbon RE, de Lorimier LP, Skorupski K, Burgess KE, Bergman PJ and Clifford CA. Response of canine cutaneous epitheliotropic lymphoma to lomustine (CCNU): a retrospective study of 46 cases (1999-2004). *Journal of Veterinary Internal Medicine* 2006; **20**: 1389–1397.
27. LeBlanc AK, Cox SK, Kirk CA, Newman SJ, Bartes JW and Legendre AM. Effects of L-Asparaginase on plasma amino acid profiles and tumor burden in cats with lymphoma. *Journal of Veterinary Internal Medicine* 2007; **21**: 760–763.
28. Veterinary Co-operative Oncology Group. Veterinary Co-operative Oncology Group-Common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Veterinary and Comparative Oncology* 2004; **2**: 194–213.
29. Abbo AH and Lucroy MD. Assessment of anemia as an independent predictor of response to chemotherapy and survival in dogs with lymphoma, 96 cases (1993-2006). *Journal of the American Veterinary Medical Association* 2007; **231**: 1836–1842.
30. Krick EL, Little L, Patel R, Shofer FS, Sorenmo K, Clifford CA, *et al.* Description of clinical and pathological findings, treatment and outcome of feline large granular lymphocyte lymphoma (1996-2004). *Veterinary and Comparative Oncology* 2008; **6**: 102–110.
31. Miller AG, Morley PS, Rao S, Avery AC, Lana SE and Olver CS. Anemia is associated with decreased survival time in dogs with lymphoma. *Journal of Veterinary Internal Medicine* 2009; **23**: 116–122.