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Lomustine, methotrexate and cytarabine chemotherapy as a rescue treatment for feline lymphoma

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Abstract

Objectives The aim of this study was to assess the efficacy and tolerability of lomustine, methotrexate and cytarabine chemotherapy as rescue treatment for feline lymphoma.

Methods The medical records of 13 cats treated with lomustine, methotrexate and cytarabine for relapsed high-grade feline lymphoma, at a single institution between 2013 and 2018, were examined. All anatomical types were included. Data were analysed using descriptive statistics.

Results Nine cats received all three drugs and four cats received only two drugs owing to progressive disease. In cats that received (or in which there was intention to treat with) all three drugs, 6/13 (46%) demonstrated a complete or partial response to chemotherapy. Treatment was generally well tolerated, although two cats experienced Veterinary Comparative Oncology Group (VCOG) grade 3 neutropenia and one cat experienced VCOG grade 3 thrombocytopenia. The median progression-free survival was 61 days (range 16–721 days).

Conclusions and relevance CHOP-(cyclophosphamide, doxorubicin, vincristine, prednisolone) and COP-based protocols are established first-line chemotherapy for feline lymphoma, but standard rescue protocols are lacking. Lomustine has become a popular single-agent option, but prolonged or cumulative myelosuppression can result in treatment delays, risking relapse. Therefore, a multidrug lomustine-based protocol may be advantageous, and, from first principles, should also better overcome resistance. This study suggests that lomustine, methotrexate and cytarabine may represent an efficacious and well-tolerated protocol for feline lymphoma rescue.

Keywords: Chemotherapy; rescue; lymphoma; lomustine; methotrexate; cytarabine

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Introduction

Lymphoma is a common malignancy in cats, encompassing a wide range of anatomical and histological subtypes.[1,2] The broad histological subtypes are low-grade lymphoma and intermediate- or high-grade lymphoma, the latter having a more aggressive clinical course.[2] Anatomical classification categories in the literature are variable.[1,3]

CHOP-(cyclophosphamide, doxorubicin, vincristine, prednisolone) or COP-based protocols are commonly used as first-line therapy for intermediate- or high-grade lymphoma in cats; reported response rates average around 60%.[3–9] Cats achieving complete remission (CR) may experience durable first remission times (7–10 months); for patients that do not achieve CR, the outcome is poorer.[3–5,7–9] In almost all cases, development of drug resistance leads to disease progression and recurrence. Rescue chemotherapy protocols with alternative agents are used following failure to re-induce remission with the first-line protocol or relapse during first-line therapy. Several single- and multi-agent rescue protocols are described for cats, used after relapse or failure to respond to COP, CHOP or other protocols (Table 1). Studies include all rescues (ie, not just second-line therapy) and response rates are variable (22–70%), but generally low,

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Table 1 Summary of published single- and multi-agent rescue protocols for feline lymphoma

Protocol	Histological type	Anatomical location	Number of cats	Overall response rate (%) (CR rate; %)	PFI for CR	Median PFI (days)	Median OST (days)
Doxorubicin-based chemotherapy[10]	Low-, intermediate- and high-grade, granular cell	Various	23	22 (9)	1 cat, 6 weeks; 1 cat, 47 months	–	–
Single-agent lomustine[11]	Low-, intermediate- and high-grade	Various	39	–	–	39	–
Mechlorethamine, vincristine, melphalan, prednisolone (MOMP)[12]	Intermediate- and high-grade	Various	12	58 (42)	62 days	22	–
Dexamethasone, melphalan, actinomycin-D, cytarabine (DMAC)[13]	High-grade	Various	19	26	–	14	17
Mustargen, vincristine, procarbazine, prednisolone (MOPP)[14]	Not specified	Various 62% gastrointestinal	38	70	–	166 among responders (CR and PR)	–

CR = complete remission; PFI = progression free interval; OST = overall survival time; PR = partial remission

and subsequent durable remissions are seldom achieved (median progression-free interval [PFI] 14–166 days).[10–14]

Single-agent lomustine has been described as both first-line treatment and rescue treatment in feline lymphoma.[11,15] In naive intermediate- and high-grade gastrointestinal lymphoma the overall response rate was 50%, with a median duration of response of 302 days (range 64–1450 days).[15] Unsurprisingly, efficacy was lower in the rescue setting with a median PFI of 180 days for gastrointestinal lymphoma and 26 days for non-gastrointestinal lymphoma.[11] Lomustine was generally well tolerated, although neutropenia was common (reported in 52%; 62% grade 3 or 4); moreover, the nadir timepoint was variable and sometimes delayed (range 1–5 weeks).[11,15]

A multi-agent lomustine-based protocol may be advantageous, potentially limiting prolonged or cumulative myelosuppression associated with lomustine, which can result in treatment delays, risking relapse. From first principles, a multi-agent protocol combining therapies with independent mechanism of action should increase the likelihood of response and minimise the evolution of drug resistance, compared with single agent protocols. Multi-agent lomustine-based rescue protocols have shown favourable efficacy in canine lymphoma,[16–18] and recently such a protocol (LOPH: lomustine, vincristine, prednisolone, doxorubicin) has been used to treat feline leukaemia virus (FeLV)-positive cats.[19] Ideally, multi-agent protocols include drugs with non-overlapping toxicities, different mechanisms of action and demonstrable specific antineoplastic effects. Methotrexate and cytarabine have been used in multi-agent first-line and rescue protocols in both canine and feline lymphoma, are generally well tolerated and less myelosuppressive than lomustine.[3,13,20–22] Based on these principles, the aim of this retrospective study was to assess the efficacy and tolerability of lomustine, methotrexate and cytarabine chemotherapy as rescue for feline lymphoma.

Materials and methods

The computerised clinical database of the University of Liverpool Small Animal Teaching Hospital was searched for feline patients treated with lomustine, methotrexate and cytarabine from January 2013 to December 2018. Patients had to meet the following inclusion criteria: (1) cytological or histological diagnosis of high-grade lymphoma; and (2) treatment in the rescue setting having failed COP or CHOP protocol as the first-line treatment. Patients were allowed to have received alternate rescue chemotherapy prior to treatment with lomustine, methotrexate and cytarabine. Cats with low-grade lymphoma were specifically excluded. All anatomical types of lymphoma were included. Patients that did not receive all

Table 2 Summary of relevant Veterinary Comparative Oncology Group – Common Terminology Criteria for Adverse Events[23]

	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia ($\times 10^9$/l)	1.5–<LLN	1–<1.5	0.5–<1	<0.5
Thrombocytopenia ($\times 10^9$/l)	100–<LLN	50–99	25–49	<25
ALT	>ULN–1.25 × ULN	>1.25 × ULN–1.5 × ULN	>1.5 × ULN – 2 × ULN	>2 × ULN
Gastrointestinal	Mild; mild clinical signs only; intervention not indicated	Moderate; minimal, outpatient or non-invasive intervention indicated; moderate limitation of ADL	Severe or medically significant but not immediately life threatening; hospitalisation indicated; significantly limiting ADL	Life-threatening consequences; urgent intervention indicated, eg, haemodynamic collapse, parenteral nutrition indicated

LLN = lower limit of normal; ALT = alanine transaminase; ULN = upper limit normal; ADL = activities of daily living

three drugs due to progressive disease and protocol discontinuation were not excluded.

Data obtained from the records included patient signalment, weight, body condition score, feline immunodeficiency virus (FIV)/FeLV status, anatomical location(s) of lymphoma, immunophenotype (if available), number of previous chemotherapy agents/protocols received, duration of first-line response and data relating to treatment with lomustine, cytarabine and methotrexate: lomustine/cytarabine/methotrexate dosage; administration of prednisolone; results of complete blood count (CBC) with associated manual differential; documented toxicity; response to treatment; progression-free survival (PFS); and reason for discontinuation.

Cats were treated with alternating lomustine (target dose of 10 mg/cat or 45 mg/m^2 PO), methotrexate (target dose of 0.5–0.6 mg/kg IV), and cytarabine (target dose of 300 mg/m^2 SC). There was a 2–3-week interval post-lomustine administration, a 2-week interval post-methotrexate and a 1–2-week interval post-cytarabine administration, at the clinician's discretion. Treatment was continued until progressive disease, or discontinued after a sustained complete remission duration, which was at the clinician's discretion. Prednisolone was administered/continued (target dosage of 1–2 mg/kg q24h or every other day) at the clinician's discretion. CBC with associated manual differential was performed prior to the administration of chemotherapy and, in some (but not all) cases, at the time of the anticipated lomustine nadir (7–10 days post-treatment). The neutrophil cut-off for treatment was 2–2.5 $\times 10^9$/l at the clinician's discretion. Measurement of ALT and other biochemistry parameters was not routinely performed, unless deemed appropriate by the clinician for patient-specific reasons (eg, monitoring azotaemia in patients with renal lymphoma).

Chemotherapy-related toxicities were graded (either by the clinician at the time or retrospectively) according to the Veterinary Comparative Oncology Group – Common Terminology Criteria for Adverse Events (Table 2).[23] Response to treatment was based on clinical signs, physical examination, measurement of palpable lesions, haematology/biochemistry (if applicable) and imaging ± cytology if performed. CR was defined as resolution of measurable disease and/or tumour-associated clinical signs, partial response (PR) as >50% but <100% decrease in measurable disease, and no response (NR) as <50% decrease or increase in measurable disease and/or worsening tumour-associated clinical signs. Response to treatment based on clinical signs, physical examination and measurement of palpable lesions was performed at every appointment. Response to treatment based on imaging ± cytology was performed at the clinician's discretion, most often after one cycle or in response to a suspicion of disease progression. PFS was defined as the time from initiation of treatment with lomustine, methotrexate and cytarabine to documentation of progressive disease. Cats that were in clinical remission at the end of the data collection or experienced lymphoma-unrelated death were censored.

Data were analysed using descriptive statistics. The Kaplan–Meier product limit method was used to estimate PFS.

Results

Thirteen cats met the inclusion criteria. The median age was 9.0 years (range 1.1–12.2 years). The median weight was 4.4 kg (range 3.1–5.8 kg). There were nine neutered males and four neutered females. A variety of breeds were represented: domestic shorthair (n = 8), Siamese (n = 2), domestic longhair (n = 1), British Blue (n = 1) and Persian (n = 1). FeLV status was assessed (antigen ELISA) in 7/13 cats, and all tested negative. FIV status was assessed (antibody ELISA) in 7/13 cats and 2/7 tested positive. Anatomical locations are shown in Table 3. High-grade

Table 3 Summary of the clinical data of cats receiving a lomustine, methotrexate and cytarabine protocol for relapsed lymphoma after relapsing CHOP or COP

Patient	Sex	Age (years)	Breed	Anatomical location	Cytology (C) / histology (H) diagnosis	FIV/FeLV status	T/B cell	Previous treatment	Duration first response post-COP/CHOP (days)	Lomustine (mg/m^2)	Cytarabine (mg/m^2)	Methotrexate (mg/kg)	Predni-solone (mg/kg)	Number of chemo-therapy treatments	Receive all three drugs; reason if not	PFS (days)	Response
1	FN	6.0	British Blue	Mediastinal	C			COP, lomustine	14	40	279	0.62	1	13	Yes	455	CR
2	MN	10.0	DSH	Abdominal and thoracic lymph nodes	H	Negative		COP	68	33	286	0.66	2	6	Yes	61	PR
3	MN	6.6	Persian	Spleen	C	Negative		COP	65	39	296	0.55	1	25	Yes	1246*	CR
4	MN	7.3	DSH	Extranodal (nasal)	H	FIV+	B	COP	58	40	289	0.61	1	3	Yes	27	NR
5	MN	10.5	DSH	Extranodal (SC)	H		B	COP, epirubicin	13	43	325	0.57	1	6	Yes	120	CR
6	MN	12.2	DSH	Extranodal (renal)	C	FIV+		COP	28	39	0	0.59	0	2	No; PD	22	NR
7	MN	11.4	DSH	Abdominal lymph nodes	C	Negative	B	CHOP	32	38	272	0.58	1	17	Yes	721	CR
8	MN	9.3	DSH	Abdominal lymph nodes	C and H		T	COP, epirubicin	44	51	305	0.49	1	4	Yes	77	NR
9	FN	4.2	Siamese	Extranodal (nasal)	H		B	COP, radiation	504	40	283	0.51	0	10	Yes	158	PR
10	MN	8.0	DLH	GIT	C			COP	21	43	286	0.60	1	4	Yes	33	NR
11	FN	9.8	DSH	GIT	C and H	Negative	B	COP	49	38	277	0	1	2	No; PD	24	NR
12	MN	9.0	DSH	Rectal	H		B	COP	29	33	273	0	1	2	No; PD	16	NR
13	FN	1.1	Siamese	Mediastinal with abdominal lymph nodes	H	Negative		CHOP	222	65	286	0	0	2	No; PD	25	NR

*Case censored from progression-free survival (PFS) analysis

FIV = feline immunodeficiency virus; FeLV = feline leukaemia virus; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; FN = female neutered; CR = complete remission; MN = male neutered; DSH = domestic shorthair; PR = partial response; NR = no response; SC = subcutaneous; PD = progressive disease; DLH = domestic longhair; GIT = gastrointestinal tract

lymphoma was diagnosed on cytology in five cases, histopathology in six cases and a combination of both in two cases. Immunophenotype was evaluated by immunohistochemistry in six cases and by PCR for antigen receptor rearrangement in one case: six were B cell and one was T cell.

All cats had received COP or CHOP as their first-line treatment. The median duration of response to first-line treatment was 44 days (range 13–504 days). The majority of cats (n = 10/13) received lomustine, methotrexate and cytarabine as their first rescue treatment used; three cats had received one other rescue protocol prior to this (two cats single-agent epirubicin and one cat single-agent lomustine; protocol duration 22–120 days). In addition, one cat with nasal lymphoma received radiation therapy (five fractions of 7 Gy) in combination with COP as a first-line treatment. Five cases were cytologically confirmed to have relapsed immediately prior to starting the lomustine, methotrexate and cytarabine-based protocol. In seven cases imaging findings supported the clinical diagnosis of relapse, but cytology was not performed. The remaining case had relapse documented by imaging and cytology prior to one of earlier rescue agents, to which the cat had not responded.

The median number of chemotherapy treatments administered as part of the lomustine, methotrexate and cytarabine protocol was four (range 2–25). Nine cats received all three drugs. Four cats received only two drugs owing to progressive disease and thus proceeding with the remainder of the protocol was deemed inappropriate by the clinician or declined by the client. The median starting doses of drugs were lomustine 40 mg/m^2 (range 33–65 mg/m^2), cytarabine 286 mg/m^2 (range 272–325 mg/m^2) and methotrexate 0.57 mg/kg (range 0.49–0.66 mg/m^2). In 11 cats, prednisolone was administered/continued at a median dose of 1 mg/kg (range 1–2 mg/kg).

Table 4 shows the toxicity experienced during the protocol. Neutropenia was documented in 6/13 (46%) cats (either at the next pretreatment visit or upon sampling at anticipated lomustine nadir); there were no grade 4 events, and neutropenia was not a dose-limiting toxicity. Neutropenia was most commonly observed following administration of lomustine and, to a lesser extent, following cytarabine (neutropenia occurred in three cats following lomustine, two cats following cytarabine, one cat following lomustine and cytarabine); no episodes of neutropenia were documented following methotrexate. Treatment delays occurred in three cats due to neutropenia (two 7-day delays following cytarabine and one 14-day delay following lomustine; neutropenia was grade 2 in two cats and grade 3 in one cat; duration of delay was at the clinician's preference). There were no episodes of febrile neutropenia or sepsis. Thrombocytopenia occurred in 2/13 cats (15%). One cat experienced grade 1 thrombocytopenia following lomustine, which did not result in a treatment delay, resolved and did not recur in absence of protocol modification. The other cat experienced grade 3 thrombocytopenia and associated clinical bleeding (haematuria, epistaxis) following cytarabine; however, this may have been due to progressive disease or chemotherapy toxicity, or both. Gastrointestinal toxicity occurred in 6/13 cats (46%): all events were low grade, the majority were hyporexia and most occurred after the administration of cytarabine.

Supportive medications, including maropitant, mirtazapine and probiotics, were dispensed at the clinician's discretion. Two cats required hospitalisation during treatment, but in both cases this was likely due to progressive disease rather than chemotherapy toxicity: cat 6 was hospitalised for 24 h owing to grade 2 gastrointestinal toxicity and was euthanased within the week following hospitalisation owing to progressive disease, while cat 13 was hospitalised for 48 h for grade 3 thrombocytopenia and grade 2 gastrointestinal toxicity; thoracic radiographs performed at the time confirmed progressive disease and the patient was euthanased.

In cats that received (or in which there was intention to treat with) all three drugs, 6/13 (46%) demonstrated a response to chemotherapy. Four of six achieved CR (in three cats response was assessed with imaging or measuring palpable lesions ± cytology; one assessed on clinical signs alone) and 2/6 achieved PR (one response assessed with abdominal ultrasound and one assessed on clinical signs alone).

The protocol was discontinued because of disease progression in 11 cats. In four cats the protocol was

Table 4 Frequency of toxicity in 13 cats receiving a lomustine, methotrexate and cytarabine protocol, graded according to Veterinary Comparative Oncology Group (VCOG) criteria[23]

Type of toxicity	Total	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	6	4	2	0	0
Neutropenia	6	2	2	2	0
Thrombocytopenia	2	1	0	1	0

The highest toxicity grade is reported for each patient. For gastrointestinal events, the highest VCOG grade among vomiting, diarrhoea or anorexia was considered

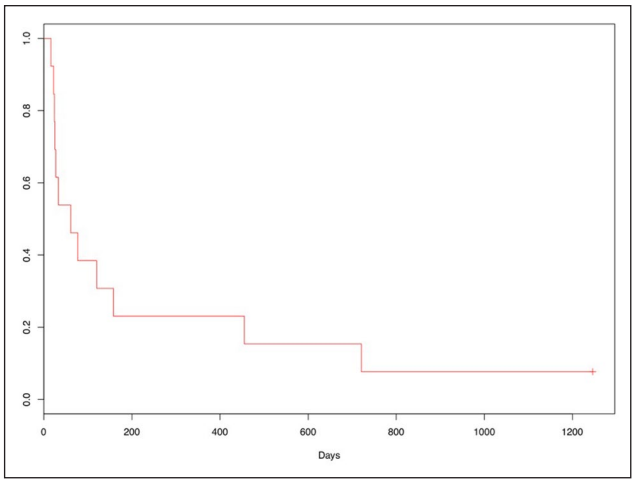

Figure 1 Kaplan–Meier plot showing the time to progression for 13 cats receiving a lomustine, methotrexate and cytarabine protocol for relapsed lymphoma

discontinued owing to progressive disease after receiving only 2/3 drugs; none of these cats received further chemotherapy treatment and all were euthanased within 5 days. In two cats protocol discontinuation was due to ongoing complete remission (after 17 and 25 chemotherapy treatments, respectively, at the clinician's discretion): one cat subsequently experienced lymphoma progression and one cat was euthanased owing to chronic kidney disease (CKD) but was in complete remission at the time (PFS 1246 days); this cat was censored from PFS. Progression of the CKD occurred after discontinuation of chemotherapy. The median PFS was 61 days (range 16–721 days) (Figure 1). The median PFS in the six responders was 307 days (range 61–721 days).

Discussion

This retrospective study reports the outcome of feline patients with relapsed lymphoma that received lomustine in combination with methotrexate and cytarabine as a multi-agent rescue treatment.

Lomustine-based rescue protocols are established in dogs[16–18] but have yet to be evaluated in cats, for which rescue options are limited. The foundation for formulating this protocol was the evidence for efficacy of single-agent lomustine in both the naive and rescue setting for feline lymphoma.[11,15] However, our clinical observation was single-agent lomustine had the potential to result in prolonged or cumulative myelosuppression creating treatment delays and risking relapse due to loss of dose intensity. Therefore, a multi-agent protocol was instigated to try and mitigate this, with the additional benefit of potentially overcoming resistance more effectively.

The response rate in our small cohort of patients was 46%. The median PFS for all cats was 61 days and the median PFS for responders was 307 days, which is consistent with the response to treatment being an established key prognostic indicator in cats.[4,5] Statistical comparison within the cohort was not performed because of the small study population. Overall survival time was not assessed in this population because some cats went on to receive additional rescue protocols and the potential confounder of owners' decisions regarding euthanasia. Comparison of response rate and response duration to other rescue protocols is inherently limited and would not yield a clinically meaningful conclusion. A simple clinical conclusion is that the response rate was modest but durable remissions were achieved in a small number of responders, with 3/13 having a PFS of >300 days.

A point of discussion is the inclusion of patients that did not receive all three drugs. Four cats did not receive all three owing to progressive disease and were subsequently euthanased within 5 days: the exclusion of these cases would have biased towards a more favourable, unrepresentative outcome. There was also some dose and dosing schedule heterogeneity within this population at the clinician's discretion mainly due to variability in the lomustine nadir. The best schedule for the protocol is unknown and assessment of a more defined schedule in future studies may be of benefit. The median starting dose of methotrexate was 0.57 mg/kg IV, which may be relatively low. The reported dose for methotrexate in cats is 0.3–0.8 mg/kg IV (normally as part of a multi-agent protocol), with 0.6–0.8 mg/kg more commonly reported.[22,24,25] Dose escalations with a target of 0.8 mg/kg may be appropriate. Administering methotrexate orally to minimise administration of injectable chemotherapy may also be a point for consideration; however, the appropriate dosage is less clear and there is the potential for variation in bioavailability.

In this study all patients received cytarabine as a single dose subcutaneously (target dose 300 mg/m^2). This route and dose was chosen because it is the predominant choice in previous multi-agent protocols involving cytarabine and is more practical in clinical practice.[13,21,26] Alvarez et al found no significant difference in response between subcutaneous or continuous rate infusion administration as part of the DMAC protocol in dogs (dexamethasone, melphalan, actinomycin D and cytosine arabinoside).[26] However, a pharmacokinetic study of cytarabine in healthy dogs showed that subcutaneous administration, compared with continuous IV administration, limits the ability to maintain steady-state concentrations and overall exposure.[27] Although the plasma concentration of cytarabine necessary to produce a clinical response in cats is unknown, rapid elimination may result in the drug being less efficacious when administered subcutaneously.

The median duration of response to first-line treatment in this population was relatively short at 44 days (range 13–504 days). Given the small data set, it was not possible to assess whether there was a relationship between response to first-line treatment and response to rescue treatment. However, given that a subset of responders

went on to achieve long-term remission it would suggest that this rescue protocol is still worth pursuing in cats with a short duration of first response. In this study, three cats received the protocol as a second rescue, which may have affected response. Future studies examining this protocol as a first rescue only may be of benefit.

Neutropenia, normally following lomustine treatment, was common (n = 6/13 [46%]), similar to the 52% reported with single-agent lomustine in naive cats with lymphoma.[15] However, in the present study the majority were grade 1 or 2, whereas Rau and Burgess reported 62% grade 3 or grade 4 with the same lomustine dosage.[15] None of the neutropenic episodes resulted in hospitalisation, but treatment delays occurred in 3/6 cats. Neutropenia occurred infrequently after cytarabine and no episodes of neutropenia were documented after methotrexate: this may support their use as part of a multi-agent protocol with lomustine to avoid further myelosuppression and associated treatment delays. An important limitation when interpreting the occurrence of neutropenia is that haematology at the time of the anticipated lomustine nadir was not performed in all cases, so the incidence of neutropenia may have been underestimated. Furthermore, given that the nadir can be highly variable in cats, the results from those that were tested may not reflect the extent of myelosuppression. Gastrointestinal toxicity was relatively common (n = 6/13 [46%]), the majority being hyporexia, but all were low grade. As the current study was retrospective, gastrointestinal toxicity may have been underestimated, particularly if low grade, as it may not have been reported by the owners or noted in the clinical records. Thrombocytopenia was uncommon (n = 2/13 [15%]) and was only clinically significant in one cat, but this may have reflected progressive disease. Distinguishing chemotherapy-induced adverse events and clinical signs in advanced lymphoma is challenging, and may lead to an overestimation of chemotherapy adverse events; in this cohort, the two patients that were hospitalised more likely required management of lymphoma clinical signs as opposed to chemotherapy toxicity.

Lomustine has been documented to cause hepatic toxicity in dogs,[28] but whether this occurs in cats remains to be determined. Dutelle et al[11] measured alanine aminotransferase (ALT) in some (but not all) patients, and seven patients experienced ALT elevation (5/23 reported episodes of elevated ALT in seven patients were grade 4); however, owing to a lack of baselines and the absence of exclusion of lymphoma, no definitive conclusion was drawn regarding the risk of hepatotoxicity. In this study, measurement of ALT was not performed frequently enough to comment on risk of hepatotoxicity; however, no cat was suspected to have suffered significant hepatotoxicity. Further work is needed to characterise the risk of hepatic toxicity in cats.

There are a number of limitations to this study: first, its retrospective nature, and, secondly, the variable timing and method of response assessment, in some cases on the basis of clinical signs and physical examination findings alone (clinical remission). Definitions of clinical remission are vague and can over- or underestimate the true degree of remission. Frequent diagnostic imaging and cytology is rarely achievable in clinical practice owing to financial constraints and clients' concerns regarding perceived invasive diagnostics in the face of a sometimes guarded prognosis. Although most cats had treatment discontinuation owing to progressive disease, two cats stopped treatment while in CR after non-standardised periods. This study also consists of only a small number of cases representing multiple anatomical subtypes, and there was some variability in drug dosages and intervals between the drugs in individual patient protocols, but it is valuable as an initial report on the use of lomustine in combination therapy for cats and augments the limited data available on for lymphoma rescue.

Conclusions

This study suggests that lomustine in combination with methotrexate and cytarabine may represent an efficacious and well-tolerated protocol for feline lymphoma rescue. Assessment of a more defined schedule in a larger population and evaluation of oral methotrexate administration may be of benefit in future studies.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). For any animals or humans individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved.

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