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Pegylated-L-asparaginase therapy for feline large cell lymphoma: 82 cases (2017–2020)

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Céline A Bik[1], Bart R Ruijter[1], Lindsay Van den Bossche[1], Erik Teske[2], Stijn JM Niessen[3] and Yaiza Forcada[3]

Abstract

Objectives The present study aimed to investigate pegylated-L-asparaginase monotherapy for feline large cell lymphoma as a potential alternative to palliative corticosteroids treatment in animals whose owners declined cytotoxic chemotherapy.

Methods A retrospective, descriptive case series of cats treated initially with pegylated-L-asparaginase as a sole therapy for feline large cell lymphoma is reported. The treatment protocol consisted of 12 intramuscular injections of pegylated-L-asparaginase with increasing intervals. If cats were unresponsive to pegylated-L-asparaginase monotherapy, a second-line treatment was initiated. Signalment, origin of lymphoma, staging, treatment, possible adverse events and follow-up data were extracted from the medical records. Responses and survival data were analysed.

Results Eighty-two cats with lymphoma of five different anatomic types were included: alimentary, abdominal extra-alimentary, peripheral nodal, nasal/nasopharyngeal and other (mediastinal, renal [solitary] and miscellaneous combined in one group for analytical purposes). The response rate was 74.1% (95% confidence interval = 63.4–83.5) with 38.3% (95% confidence interval = 27.8–48.8) in complete remission. The median disease-free period and calculated overall survival time were 70 days (12–1702+) and 79 days (1–1715+), respectively. The response rate was significantly correlated with the origin of the lymphoma and the combined group had a significantly lower response rate ($P = 0.035$). Twenty-four cats were also treated with corticosteroids. There was no significant difference in outcomes between the group treated with or without corticosteroids. Adverse events were present in a small number of cats (14/82). The majority of these adverse events were mild to moderate in 5/14 cats; however, the adverse events were severe enough to cause discontinuation of therapy.

Conclusions and relevance Based on the response rate and median disease-free period, treatment with pegylated-L-asparaginase is inferior when compared with historical chemotherapy protocols. However, some cats demonstrated an exceptional long disease-free period. Therefore, pegylated-L-asparaginase could be offered as an alternative to corticosteroid therapy alone. Further studies are needed to evaluate the additional benefit over palliative corticosteroid monotherapy.

Keywords: Lymphoma; lymphosarcoma; peg-asparaginase; pegylated asparaginase; Oncaspar; prednisolone

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Introduction

Feline lymphoma can be classified by anatomic location (mediastinal, alimentary, multicentric and others, such as renal, nasal and ocular),[1,2] by cell size (small, intermediate or large)[3] and most recently by immunohistochemical characteristics.[4] The median age of presentation is 11 years but with a wide range.[5,6]

The mainstay treatment option for lymphoma remains multiagent cytotoxic chemotherapy,[7–15] with

[1]Medisch centrum voor dieren Amsterdam, Amsterdam, The Netherlands
[2]Department of Clinical Sciences, Veterinary Faculty, University of Utrecht, Utrecht, The Netherlands
[3]Veterinary Specialist Consultations, Hilversum, The Netherlands

Corresponding author:
Céline A Bik DVM, Medisch centrum voor dieren Amsterdam, Isolatorweg 45, Amsterdam, 1014AS, The Netherlands
Email: celine.bik@anicura.nl

glucocorticoids being used when cytotoxic chemotherapy is declined. Reported overall response rates (ORRs) for feline lymphoma of various origins treated with different chemotherapy protocols range widely from 40% to 95%, and median overall survival times (OSTs) range from 50 days to 388 days.[7–16] Median OST for feline lymphoma treated with corticosteroids alone is not published, contrary to dogs where the median OST (range) is reported to be 31–53 days.[17]

Cat owners can be reluctant to use cytotoxic chemotherapy for different reasons, including concerns about contamination of the home environment, especially with small children, during pregnancy or when trying to conceive, or concerns about the potential adverse events (AEs), with reported rate of AEs of up to 87%.[18] The environmental hazard for owners while caring for pets being treated with chemotherapy is poorly documented, although contamination of the home environment has been reported.[19–21]

L-Asparaginase causes apoptosis of asparagine synthetase-deficient tumour cells by depletion of asparagine. It is minimally myelosuppressive, has few AEs, is not cytotoxic, teratogenic or mutagenic, and it is not considered hazardous.[22,23] Asparaginase is commonly used as part of multidrug chemotherapy protocols in people with leukaemia, although previously available *Escherichia coli*-derived asparaginase use has been limited by frequent toxicities and development of hypersensitivity reactions and neutralising antibodies.[24,25] Therefore, a pegylated (PEG) form of asparaginase was produced. PEG-L-asparaginase (PEGasp) has a longer half-life and is associated with decreased immunogenicity.[26] In canine lymphoma, PEGasp was reported to be as effective as L-asparaginase without significant AEs.[27,28] A recent study confirmed the effectiveness of PEGasp in addition to a modified cyclophosphamide, vincristine and prednisolone (COP) regime in feline patients.[29]

The objective of this study was to investigate the efficacy of PEGasp monotherapy for feline intermediate and large cell lymphoma of different anatomic locations as a potential alternative to palliative corticosteroids treatment in animals whose owners declined cytotoxic chemotherapy.

Materials and methods

Study population

This retrospective study included 82 client-owned cats with lymphoma that were presented to one referral hospital (2017–2020). Ethical and general approval for the performance of this retrospective study was awarded by the institutional ethical committee (approval no. MCD-2001). The cats were examined by supervised residents, European board-certified and/or national specialists.

Data collection

The EasyVet (K Care Healthcare Solutions) database was searched using the terms 'feline lymphoma', 'Oncaspar' and 'peg-asparaginase'. Cats with intermediate or large cell lymphoma diagnosis, peg-asparaginase therapy, palpable lesions on physical examination and/or clear lymphoma-related clinical signs were included in the study.

Exclusion from the study was based on unconfirmed diagnosis, concurrent or previous cytotoxic chemotherapy, previous L-asparaginase therapy, deviation from treatment protocol or lost to short-term follow-up. Concurrent steroid treatment was allowed. Follow-up information was collected either from hospital records or from referring veterinarian's records. The raw data can be found in Table S1 in the supplementary material.

Diagnosis and staging

Signalment, cytological or histological diagnosis, anatomical location(s) of lymphoma, staging, response to therapy and occurrence of AEs were recorded, along with feline immunodeficiency virus/feline leukaemia virus (FIV/FeLV) status and immunophenotype only when available.

Staging of the lymphoma patients was performed based on one or more of the following: physical examination, abdominal ultrasound, thoracic radiographs, serum biochemistry, complete blood count and PCR assessment of antigen receptor gene rearrangement test, if performed. Cats with abdominal disease underwent abdominal ultrasonography. Cytology of the liver and spleen was not routinely performed. Thoracic radiographs were performed in cats with mediastinal lymphoma.

Treatment protocol

The PEGasp monotherapy was offered as an alternative to corticosteroid therapy alone when owners declined chemotherapy treatment. If cats were unresponsive to PEGasp monotherapy, cytotoxic treatment was offered again. The treatment protocol consisted of intramuscular injections with PEGasp (Oncaspar; Les Laboratoires Servier) (powder for injection, after reconstitution 750 IU/ml, conserved at 4°C for a maximum of 14 days) at a dose of 500 IU/m^2 (30–40 IU/kg) according to a 12-injection protocol administered in weeks 0, 2, 4, 6, 9, 12 15, 18, 22, 26, 30 and 34.

Initial treatment was continued if cats showed complete remission or partial remission associated with a good quality of life and the owner's refusal to transfer to chemotherapy. Owners were offered to continue treatment indefinitely after the 12th injection.

Follow-up

Follow-up consisted of recheck consultations at the time of the next treatment. The maximum response to PEGasp was defined as complete remission (CR; 100% regression of measurable lesion[s] and clinical signs, excluding imaging and cytology), partial remission (PR; less than 100% but more than 50% regression of disease and partial improvement of clinical signs) and no response (less than

50% regression or growth in size of the original lesion or development of new lesions or clinical signs). Restaging through imaging and/or cytology was not routinely performed during or after the treatment. For evaluation purposes, only patients with palpable disease or clear clinical signs were included in the study.

AEs were classified using standardised terminology into grades 1–5 according to the Veterinary Co-operative Oncology Group–Common Terminology Criteria for AEs (VCOG-CTCAE; see Table S2 in the supplementary material).[30] Response rates (RRs), OST and disease-free period (DFP) were determined. To assess the response to PEGasp, clinically measurable tumour lesions and the absence of clinical signs were measured. Because imaging and endoscopy were not always used for this re-evaluation, remissions were expressed as clinical remissions.

Statistical analysis

Differences in the RR between groups were evaluated by χ^2 tests. Survival curves were drawn with the Kaplan–Meier method and comparisons of groups of survival data were made using the log-rank test. Survival time was calculated as the interval from start of treatment to death or to the date on which the cat was last known to be alive, including all cats and counting only deaths due to lymphoma as events. For cats in which there was a CR, the DFP was calculated as the interval from the start of treatment to relapse or to the date on which the cat was last known to be free of disease, counting only relapses as events. Cats were censored from overall survival analysis if they were still alive at the time of analysis, or if they were lost to follow-up. Cats were censored from DFP analysis if a recurrence had not occurred. For improving comparisons, the anatomic types with small numbers were grouped together to assess response (ie, miscellaneous, renal and mediastinal). Statistical significance was set at $P \leqslant 0.05$, or a corrected P value when applying sequential testing. All calculations were performed using SPSS, version 27.0 (IBM).

Results

The initial search included 270 cats. After applying the inclusion and exclusion criteria, 82 cats were included in the study. Two cats were lost to long-term follow-up but completed the treatment protocol.

Patient characteristics

All patient characteristics are presented in Table 1. No stage 5 disease was identified, although haematology was not routinely performed.

Response

The maximum response during the entire therapy was recorded for all cats but one. This cat (alimentary lymphoma) died 1 day after treatment initiation and was included in the overall survival but excluded from the RR analyses. The number of treatments varied from 1 to 30, with a median of three injections.

ORR was 74.1% (95% confidence interval = 63.4–83.5%), with CR in 38.3% (95% confidence interval = 27.8–48.8%) of cats. RR per anatomical location are reported in Table 2.

RR was significantly lower for the subgroup 'other' ($P = 0.035$) compared with the standard types. No additional statistically significant differences were observed. Sex ($P = 0.284$) and stage ($P = 0.215$) did not have a significant influence on response.

Median DFP was 70 days (13–1702+) with a 1-year disease-free percentage of 21.5% (Figure 1). Median calculated OST was 79 days (–1715+) with a 1-year survival rate of 20.8%.

There was no significant difference between the median OST or DFP with the different anatomic locations of lymphoma (Table 3).

Seven cats completed the entire treatment protocol (8.5%). Five cats had alimentary lymphoma, two with nasal lymphoma. All but one of these cats showed CR, and the remaining cat was in PR. Two cats were lost to follow-up after treatment was completed, both in CR at their last visit. Three cats were still alive at the time of writing.

Additional corticosteroids were used in 29% (n = 24) of cases, in varying doses. The rationale for corticosteroid use is listed in Table 4. There was no significant difference in RR between outcomes of cats treated with or without steroids ($P = 0.468$). In addition, there were no significant differences in remission times ($P = 0.901$) and OST ($P = 0.822$).

At the time of data collection, 74 cats had died, six cats were alive and two cats were lost to follow-up. In 71 cases, the death of the cat was lymphoma-related. Three cats died of unrelated or unknown causes, all showing CR at the time (21 days, 106 days and 1260 days after diagnosis). Nineteen cats (23%) with an underwhelming response were switched to other treatment options, either chemotherapy or radiation.

AEs

AEs were reported in 14/82 cats (17%) and are shown in Table 5. The number of injections varied from 1 to 12 with a median of 2.5 treatments per cat. Although AEs were more often noted in castrated males (11/14) than spayed females (3/14), this difference was not significant ($P = 0.270$). AEs were reported in alimentary (n = 6), nasal (n = 3), peripheral nodal (n = 2), abdominal extra-alimentary (n = 2) and renal lymphoma (n = 1). Stage was uniformly represented. The severity of AEs were the sole reason for discontinuation of therapy in 36% (5/14). One cat was euthanased 1 day after the first PEGasp treatment due to acute collapse, bradycardia and dyspnoea. It was censored from the response cohort but included in the group of patients experiencing AEs and OST. In one

Table 1 Summary of patient characteristics and clinical data of the 82 cats

Variable and category	n	%
Median age (years)		
10 (± 3.8)		
Sex		
Male	54	66
Female	28	34
Breed		
Domestic shorthair	53	65
Maine Coon	8	10
Blue Russian	3	4
British Shorthair	3	4
Burmese	2	2
Domestic longhair	2	2
Siamese	2	2
Sphynx	2	2
Other (seven breeds: n = 1)	7	9
Anatomical location		
Alimentary lymphoma	24	29
Nasal and nasopharyngeal	21	26
Peripheral nodal	19	23
Abdominal extra-alimentary	9	11
Other	9	11
Renal	4	5
Mediastinal	4	5
Miscellaneous	1	1
Stage		
I	25	30
II	14	17
III	30	37
IV	13	16
V	0	0
Substage based on clinical signs		
Without systemic signs	0	0
With systemic signs	82	100
FeLV/FIV status		
FeLV positive	3	4
FIV positive	1	1
Negative	6	7
Unknown	72	88
Diagnosis		
Cytology	56	68
Histology	26	32
Immunophenotype		
B-cell	7	8
T-cell	0	0
Unknown	75	92
Concurrent treatment with corticosteroids	8	33
Prior and during PEGasp therapy	16	66
Started during PEGasp therapy		

PEGasp = pegylated-L-asparaginase; FeLV = feline leukaemia virus; FIV = feline immunodeficiency virus

case, escalation of the AE was seen on repeated dosing: hyporexia leading to anorexia. Pruritus was mild and associated with repeated administrations of PEGasp.

The median (range) AE duration was 5 (1–14) days, the longest were hyporexia and lethargy. The time to development AEs was reported inconsistently. In seven cases (50%), treatment was started to mitigate the AEs; antiemetics (n = 3), appetite stimulants (n = 2), corticosteroids (n = 3), laxatives (n = 1), analgesics (n = 2) or intravenous fluids (n = 2).

In four cases, the AEs possibly led to death. Three patients developed severe anorexia requiring hospitalisation and supportive treatment with oesophageal feeding tube (n = 1), or euthanasia (n = 2) when owners were unwilling or unable to hospitalise their cat. In two cats, the anorexia was mild after the first injection, requiring oral supportive medication. In both cases, the second injection was given because of good tumour response, resulting in worsening anorexia. One cat with a feeding tube was discharged, only to return in a soporous condition with bradycardia and hypothermia 2 days after the second PEGasp injection; euthanasia was therefore elected. One cat with suspected tumour lysis syndrome resulting in cardiovascular collapse was euthanased following the first injection; the owners declined diagnostics at that stage. Necropsy was declined in all cats.

Discussion

The PEGasp monotherapy was used to treat cats with medium and large cell lymphoma of a variety of anatomic locations, as an alternative to corticosteroids when owners declined cytotoxic therapy. The results of the present study indicate that PEGasp monotherapy results in complete or partial clinical response in 74.1% of cases, although it appears to result in a short median DFP (70 days) and median overall survival (79 days). It is worth mentioning the exceptional responses that were present (⩾1715 days) in three of the 31 cats with a CR. Significant AEs were noted in the study (14/82; 17%) with several patients requiring discontinuation of the treatment protocol (6/82; 7%) and four of these dying as a potential result of the AEs. The treatment protocol was completed by only 8.5% of the study population (7/82).

The CR rate does not correspond with cytotoxic chemotherapy studies, with reported CRs between 60% and 76.9%.[7,10,12,16] The short duration of responses could be related to the development of anti-asparaginase antibodies, neutralising the asparaginase and resulting in rebounding of amino acids in serum, as seen in people, and recently confirmed in dogs.[28,31] To date, this has not been confirmed in cats.

Inherent to the study design, direct comparison with other treatments cannot be made; however, the present results (median OST = 79 days, median DFP 70 = days) are less favourable than reports of cytotoxic treatments.[7,8,10–12,14–16]

Table 2 Response rates associated with different anatomical locations of lymphoma

Anatomical location	n	Response			
		ORR	CR	PR	No response
Alimentary lymphoma	23	20 (83)	12 (50)	8 (33)	3 (13)
Nasal and nasopharyngeal	21	20 (95)	10 (48)	10 (48)	1 (5)
Peripheral nodal lymphoma	19	11 (58)	4 (21)	7 (37)	8 (42)
Abdominal extra-alimentary	9	7 (78)	3 (33)	4 (44)	2 (22)
Other	9	3 (33)	1 (11)	2 (22)	6 (66)

Data are n (%)
ORR = overall response rate; CR = complete remission; PR = partial remission

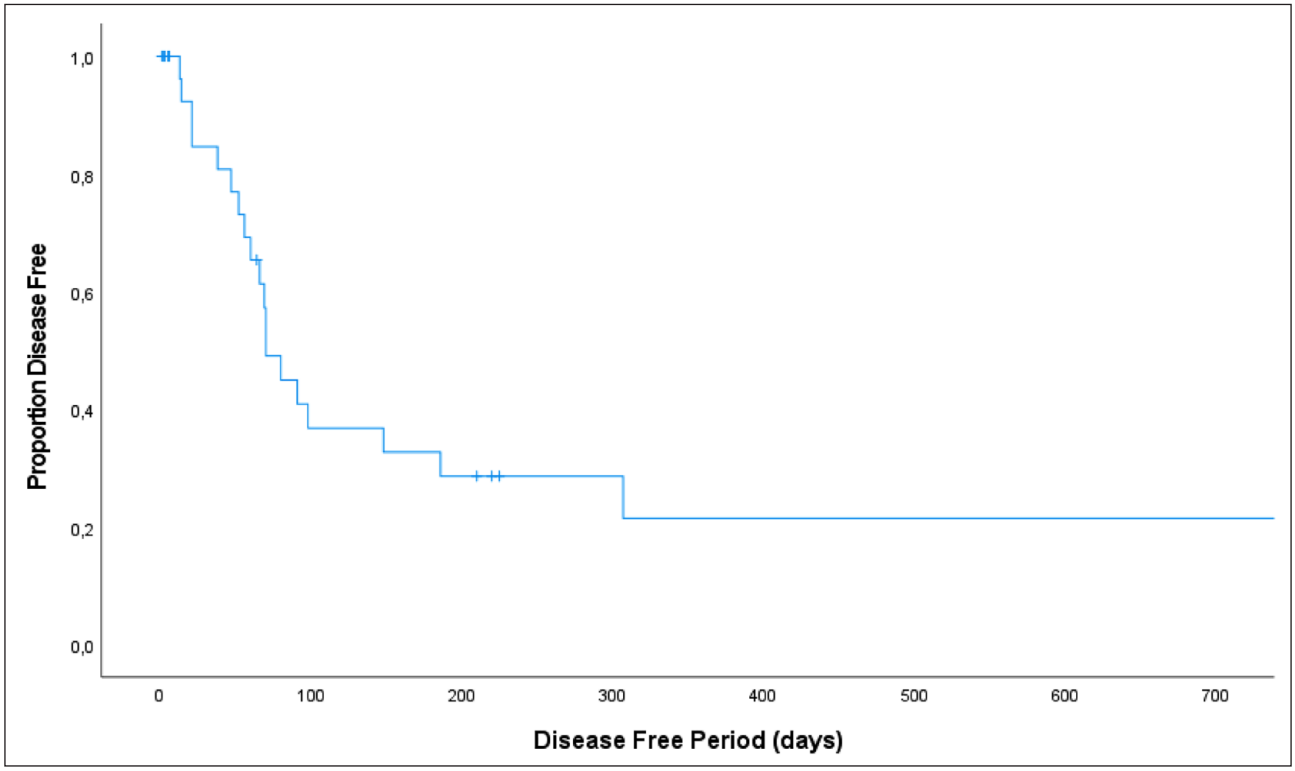

Figure 1 Disease-free survival in 31 cats with lymphoma treated with pegylated-L-asparaginase and in complete remission

Table 3 Median disease-free period and overall survival time split by the different anatomical locations of lymphoma

Lymphoma based on anatomical location	DFP		OST	
	n	Median (days)	n	Median (days)
Alimentary lymphoma	12	70	24	65
Nasal and nasopharyngeal lymphoma	10	52	21	100
Peripheral nodal lymphoma	5	148	19	94
Abdominal extra-alimentary lymphoma	3	56	9	36
Other types of lymphoma	1	98	9	147

DFP = disease-free period; OST = overall survival time

Table 4 Rationale for corticosteroid use during pegylated-L-asparaginase treatment

Rationale for corticosteroid use	n (%)
Underwhelming response with PEGasp monotherapy	12 (50)
Prior to lymphoma diagnosis	
Due to lymphoma-related disease	5 (21)
Due to unrelated diseases (inflammatory airway disease, pemphigus foliaceus, allergic skin disease, IMHA)	4 (17)
Heavy tumour burden/severe illness	2 (8)
Treatment of PEGasp AEs (pruritus)	1 (4)

PEGasp = pegylated-L-asparaginase; IMHA = immune mediated hemolytic anaemia; AEs = adverse events

DFP times are hard to compare between the different anatomic locations because of the small sizes of the subpopulations, and although there appears to be an absolute difference between the groups, it is not significant.

Median OST of corticosteroid treatment alone has not been described in a large population of cats with lymphoma. However, a study by Williams et al[32] reported a median OST of 42 days using corticosteroid treatment in nine cats with renal lymphoma and Taylor et al[33] described a median OST of 60 days in 10 cats. There are a few studies describing survival times in dogs treated with corticosteroids alone; these show MSTs ranging from 31 to 53 days with a maximum individual survival of 240 days.[17,34,35] It would be interesting to explore the life expectancy in cats treated with steroids, for comparison with PEGasp monotherapy. Although specific studies in cats with lymphoma are lacking, most AEs associated with corticosteroids are known to be mild in severity, such as polyphagia and weight gain, although more severe AEs can be seen with longer duration of treatment, mainly secondary infections and development of diabetes mellitus.[36]

In 29% (n = 24) of the cases, there was concurrent use of corticosteroids for different reasons. No significant difference in DFP between both groups was found. The corticosteroids were used for different reasons. Because corticosteroids have also been used in cases with an underwhelming success for PEGasp, a comparison of observations based on PEGasp alone and PEGasp with corticosteroids was difficult. A recent study regarding the additional effect of PEGasp in a modified COP regimen by Krupa et al[29] noted that pre-treatment with corticosteroids was a positive prognostic factor for response to PEgasp, although the group treated with steroids was small. In humans, corticosteroids decrease the immune response to PEGasp and therefore decrease the development of neutralising antibodies.[24,25] Overall, we concluded that the concurrent use of corticosteroids did not influence the outcome of the PEGasp treatment in the present study.

AEs with cytotoxic chemotherapy are reported in 47–65% of cases; commonly gastrointestinal or haematological in origin, although rarely grade 4 or 5.[7,37,38] AEs can also be present in cats treated with corticosteroids, although most are mild in severity.[36] The frequency of AEs observed in the present study (17%) was low compared with cytotoxic treatment; however, the AEs seen were markedly higher in grade. Because all cats with severe AEs were already severely ill from the lymphoma in the present study, it was difficult to truly differentiate between the AE and the disease itself. In most of these cases, however, the clinical signs were clearly present after treatment, and repeated or worsened with additional treatments. Some AEs were considered unlikely to be related to lymphoma (pruritus, alopecia) and were assumed to be true treatment-related AEs. All cats with

Table 5 Overview of the different types of adverse events, frequency and grade, according to VCOG-CTCAE

Type of toxicity	Number of episodes					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (%)
Gastrointestinal						
Hyporexia	1	2				3 (16)
Anorexia			2		2	4 (21)
Vomiting		1	1			2 (10)
Obstipation		1				1 (6)
Lethargy	2		1			3 (16)
Skin						
Pruritis	2	1				3 (16)
Localised alopecia		1				1 (6)
Circulatory shock or suspected tumour lysis syndrome					2	2 (10)

VCOG-CTCAE= Veterinary Comparative Oncology Group–Common Terminology Criteria for Adverse Events

AEs showed clear response to treatment, apart from the cat that died 1 day post-injection, reducing the chance of those clinical signs being related to lymphoma.

Pancreatitis, as reported in people treated with PEGasp,[39] was not reported in the present study as an AE; however, because none of the cats with gastrointestinal AEs underwent further diagnostics, this cannot be excluded. To our knowledge, there are no studies available that look specifically at the rate of AEs of L-asparaginase vs PEGasp in cats; however, in dogs, there were no reported AEs with PEGasp, in contrast to obvious AEs with L-asparaginase treatment.[27] There are no reported hypersensitivity reactions in cats treated with L-asparaginase.[40]

Since this is a retrospective study, the performed staging was not standardised for every cat. In some cases, staging was minimal, often due to financial constraints. In most cases, no restaging was performed, impeding further observations. Although an attempt was made to minimise the impact of this by only including cats with palpable disease and/or significant clinical signs, more objective follow-up data would have been desirable.

There is a potential selection bias. Because only cats from owners declining cytotoxic chemotherapy were included, it could be hypothesised that these owners were less likely to put their cat through a protracted treatment course. Additionally, because they did not want to pursue other treatment options, the current treatment might have been given for longer when success proved underwhelming, compared with owners who wanted to switch to regular treatment. Nevertheless, it is still worth investigating the effect of this therapeutic option in the search for different options to offer to treat different cat–owner combinations.

Retroviral testing was infrequently performed; thus, it might influence the observations that were made. Previously, FeLV infection was considered a major risk factor for developing lymphoma and leukaemia, but even with decreasing incidence over recent decades, the incidence of lymphoma is rising.[5,41] The Netherlands is among the lowest tested countries for FeLV infection, hence prevalence,[42] and FeLV positivity is present in less than 5% of the Dutch feline lymphoma cases.[12,16] Therefore, it is unlikely that FeLV was a significant comorbidity.

PEGasp has a high financial impact compared with corticosteroids; however, for average-sized cats, the costs are similar to the costs of cytotoxic chemotherapy over the long term in our clinic. Important advantages of PEGasp treatment compared with chemotherapy include that there is no need for additional tests such as haematology, it is a well-tolerated treatment, even in fractious cats, and there is an absence of environmental hazards.

Starting with PEGasp is an interesting way to introduce antineoplastic therapy to chemotherapy-hesitant owners: 19 owners (23%) decided to switch to cytotoxic treatment after underwhelming results with PEGasp. These owners would most likely have treated their cats with corticosteroids otherwise, possibly reducing life expectancy. It is not known how these cats respond to chemotherapy compared with PEGasp-negative cats. PEGasp could also be an alternative for owners of difficult-to-medicate pets because it does not involve tablets and the injections are well tolerated.

Conclusions

The ORR to therapy was, as expected, somewhat lower than existing multi-drug cytotoxic treatment protocols, although there was evidence of a good response in a proportion of cats, and there was a small subset of cats that showed exceptional long disease-free intervals and overall survival. The quality of life was generally good and the rate of AEs was lower than with cytotoxic drug protocols. For owners declining cytotoxic treatment, PEGasp monotherapy could be an alternative to palliative corticosteroid treatment and it may encourage some owners to decide to move over to chemotherapy, when they would have initially refused. Given the impact of cytotoxic chemotherapy on the wellbeing of the cats and their families, future studies are warranted to continue to explore the impact of alternative options to treat this common disease in cats, including the comparison between response to single agent PEGasp and corticosteroids, also with regard to AEs.

Supplementary material The following files are available as supplementary material:
Table S1: Patient data sheet
Table S2: Veterinary Comparative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats.

Author note The abstract of this study was presented at BSAVA Congress, Manchester 2023.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although

not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iDs Céline A Bik https://orcid.org/0009-0006-3039-0339
Bart R Ruijter https://orcid.org/0000-0002-9063-0238

References

1 Hardy WD Jr. **Hematopoietic tumors of cats.** *J Am Anim Hosp Assoc* 1981; 17: 921–940.
2 Mooney SC and Hayes AA. **Lymphoma in the cat: an approach to diagnosis and management.** *Sem Vet Med Surg (Small Anim)* 1986; 1: 51–57.
3 Valli VE, Jacobs RM, Norris A, et al. **The histologic classification of 602 cases of feline lymphoproliferative disease using the National Cancer Institute working formulation.** *J Vet Diagn Invest* 2000; 12: 295–306.
4 Wolfesberger B, Skor O, Hammer SE, et al. **Does categorisation of lymphoma subtypes according to the World Health Organization classification predict clinical outcome in cats?** *J Feline Med Surg* 2017; 19: 897–906.
5 Louwerens M, London CA, Pedersen NC, et al. **Feline lymphoma in the post-feline leukemia virus era.** *J Vet Intern Med* 2005; 19: 329–335.
6 Collette SA, Allstadt SD, Chon EM, et al. **Treatment of feline intermediate-to high-grade lymphoma with a modified university of Wisconsin–Madison protocol: 119 cases (2004–2012).** *Vet Comp Oncol* 2016; 14 Suppl 1: 136–146.
7 Simon D, Eberle N, Laacke-Singer L, et al. **Combination chemotherapy in feline lymphoma: treatment outcome, tolerability, and duration in 23 cats.** *J Vet Intern Med* 2008; 22: 394–400.
8 Mooney SC, Hayes AA, MacEwen EG, et al. **Treatment and prognostic factors in lymphoma in cats: 103 cases (1977–1981).** *J Am Vet Med Assoc* 1989; 194: 696–702.
9 Zwahlen CH, Lucroy MD, Kraegel SA, et al. **Results of chemotherapy for cats with alimentary malignant lymphoma: 21 cases (1993–1997).** *J Am Vet Med Assoc*, 1998; 213: 1144–1149.
10 Vail DM, Moore AS, Ogilvie GK, et al. **Feline lymphoma (145 cases): proliferation indices, cluster of differentiation 3 immunoreactivity, and their association with prognosis in 90 cats.** *J Vet Intern Med* 1998; 12: 349–354.
11 Waite AH, Jackson K, Gregor TP, et al. **Lymphoma in cats treated with a weekly cyclophosphamide-, vincristine- and prednisone-based protocol: 114 cases (1998–2008).** *J Am Vet Med Assoc* 2013; 242: 1104–1109.
12 Teske E, Van Lankveld AJ and Rutteman GR. **Intraperitoneal antineoplastic drug delivery: experience with a cyclophosphamide, vincristine and prednisolone protocol in cats with malignant lymphoma.** *Vet Comp Oncol* 2014; 12: 37–46.
13 Mahony OM, Moore AS, Cotter SM, et al. **Alimentary lymphoma in cats: 28 cases (1988–1993).** *J Am Vet Med Assoc* 1995; 207: 1593–1598.
14 Jeglum KA, Whereat A and Young K. **Chemotherapy of lymphoma in 75 cats.** *J Am Vet Med Assoc* 1987; 190: 174–178.
15 Fabrizio F, Calam AE, Dobson JM, et al. **Feline mediastinal lymphoma: a retrospective study of signalment, retroviral status, response to chemotherapy and prognostic indicators.** *J Feline Med Surg* 2014; 16: 637–644.
16 Teske E, van Straten G, van Noort R, et al. **Chemotherapy with cyclophosphamide, vincristine and prednisolone (COP) in cats with malignant lymphoma: new results with an old protocol.** *J Vet Intern Med* 2002; 16: 179–186.
17 Mortier F, Daminet S, Vandenabeele S, et al. **Canine lymphoma: a retrospective study (2009–2010).** *Vlaams Diergeneeskd Tijdschr* 2012; 81: 341–351.
18 Tzannes S, Hammond MF, Murphy S, et al. **Owners 'perception of their cats' quality of life during COP chemotherapy for lymphoma.** *J Feline Med Surg* 2008; 10: 73–81.
19 Yuki M, Takase K, Sekine S, et al. **Buffering the pain of local anaesthetics: a systematic review.** *J Nurs Educ Prac* 2014; 4: 16.
20 Meijster T, Fransman W, Veldhof R, et al. **Exposure to antineoplastic drugs outside the hospital environment.** *Ann Occup Hyg* 2006; 50: 657–664.
21 Smith AN, Klahn S, Phillips B, et al. **ACVIM small animal consensus statement on safe use of cytotoxic chemotherapeutics in veterinary practice.** *J Vet Intern Med* 2018; 32: 904–913.
22 Chun R, Garrett L and MacEwen EG. **Cancer chemotherapy.** In: Withrow SJ and MacEwen EG (eds) Small animal clinical oncology. Philadelphia, PA: WB Saunders; 2001: pp 92–119.
23 Connor TH, MacKenzie BA, De Bord DG, et al. **NIOSH list of antineoplastic and other hazardous drugs in healthcare settings.** DHHS publication; no. (NIOSH) 2016-161, 2016. https://stacks.cdc.gov/view/cdc/41372 (2016, accessed 10 July 2022)
24 Bender C, Maese L, Carter-Febres M, et al. **Clinical utility of pegaspargase in children, adolescents and young adult patients with acute lymphoblastic leukemia: a review.** *Blood Lymphat Cancer* 2021; 11: 25.
25 Bade NA, Lu C, Patzke CL, et al. **Optimizing pegylated asparaginase use: an institutional guideline for dosing, monitoring and management.** *J Oncol Pract* 2020; 26: 74–92.
26 Zeidan A, Wang ES and Wetzler M. **Pegasparaginase: where do we stand?** *Expert Opin Biol Ther* 2009; 9: 111–119.
27 Teske E, Rutteman GR, van Heerde P, et al. **Polyethylene glycol-L-asparaginase versus native L-asparaginase in canine non-Hodgkin's lymphoma.** *Eur J Cancer* 1990; 26: 891–895.
28 Feenstra LR, Gehring R, van Geijswijk IM, et al. **Evaluation of PEG-L-asparaginase in asparagine suppression and anti-drug antibody development in healthy Beagle dogs: a multi-phase preclinical study.** *Vet J* 2022; 286. DOI: 10.1016/j.tvjl.2022.105854.

29 Krupa A, de Vos J, Van Eetvelde L, et al. **Pegylated asparaginase in feline high-grade lymphoma: clinical results of single injection and continued incorporation into a modified COP regimen.** *J Feline Med Surg* 2022; 24: e203–e213.
30 Leblanc AK, Atherton M, Bentley RT, et al. **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.** *Vet Comp Oncol* 2004; 2: 195–213.
31 Avramis VI and Panosyan EH. **Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future.** *Clin Pharmacokinet* 2005; 44: 367–393.
32 Williams AG, Hohenhaus AE and Lamb KE. **Incidence and treatment of feline renal lymphoma: 27 cases.** *J Feline Med Surg* 2021; 23: 936–944.
33 Taylor SS, Goodfellow MR, Browne WJ, et al. **Feline extranodal lymphoma: response to chemotherapy and survival in 110 cats.** *J Small Anim Pract* 2009; 50: 584–592.
34 Squire RA, Bush RM, Melby EC, et al. **Clinical and pathologic study of canine lymphoma: clinical staging, cell classification, and therapy.** *J Natl Cancer Inst* 1973; 51: 565–574.
35 Tozon N, Samardzija P and Prijic S. **Canine lymphoma: cytologic study and response to therapy.** *Slov Vet Zb* 2006; 43: 127–133.
36 Simpson DL and Burton GG. **Use of prednisolone as monotherapy in the treatment of feline pemphigus foliaceus: a retrospective study of 37 cats.** *Vet Dermatol* 2013; 24: 598–601.
37 Sunpongsri S, Kovitvadhi A, Rattanasrisomporn J, et al. **Effectiveness and adverse events of cyclophosphamide, vincristine, and prednisolone chemotherapy in feline mediastinal lymphoma naturally infected with feline leukemia virus.** *Animals* 2022; 12. DOI: 10.3390/ani12070900.
38 Dos Santos Cunha SC, Silva FB, Corgozinho KB, et al. **Retrospective study of adverse events of chemotherapy in cats.** *Acta Sci Vet* 2018; 46: 1–12.
39 Alvarez OA and Zimmerman G. **Pegaspargase-induced pancreatitis.** *Med Pediatr Oncol* 2000; 34: 200–205.
40 Blake MK, Carr BJ and Mauldin GE. **Hypersensitivity reactions associated with L-asparaginase administration in 142 dogs and 68 cats with lymphoid malignancies: 2007–2012.** *Can Vet J* 2016; 57: 176.
41 Dorn CR, Taylor DO and Hibbard HH. **Epizootiologic characteristics of canine and feline leukemia and lymphoma.** *Am J Vet Res* 1967; 28: 993–1001.
42 Studer N, Lutz H, Saegerman C, et al. **Pan-European study on the prevalence of the feline leukaemia virus infection–reported by the European Advisory Board on Cat Diseases (ABCD Europe).** *Viruses* 2019; 11. DOI: 10.3390/v11110993.