Treatment of feline lymphoma using a 12-week, maintenance-free combination chemotherapy protocol in 26 cats

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Abstract
The aim of this prospective clinical trial was to investigate the efficacy and toxicity of a short-term, maintenance-free chemotherapy protocol in feline lymphoma. Twenty-six cats with confirmed diagnosis of high-/intermediate-grade lymphoma were treated with a 12-week protocol consisting of cyclic administration of L-asparaginase, vincristine, cyclophosphamide, doxorubicin and prednisolone. Complete (CR) and partial remission (PR) rates were 46 and 27%, respectively. Median duration of first CR was 394 days compared with a median PR duration of 41 days. No factor was identified to significantly influence the likelihood to reach CR. Overall survival amounted to 78 days (range: 9–2230 days). Median survival in CR cats was 454 days and in PR cats was 82 days. Toxicosis was mainly low grade with anorexia seen most frequently. In cats achieving CR, maintenance-free chemotherapy may be sufficient to attain long-term remission and survival. Factors aiding in prognosticating the likelihood for CR, strategies enhancing response and targeting chemotherapy-induced anorexia need to be identified in future.

Keywords
cat, remission, short-term chemotherapy, survival, toxicosis

Introduction
Lymphoma is one of the most frequent neoplasms in the cat. With an estimated annual incidence of 160–200 per 100 000 individuals, lymphoma accounts for about 90% of feline haematopoietic tumours.1–4 In spite of a decreasing number of feline leukaemia virus (FeLV) infections within the last decades, the incidence of feline lymphoma has increased.4 As in the dog chemotherapy is the treatment of choice for most lymphoma forms of the cat.5 There are diverse multiagent and single-agent chemotherapy protocols with different duration times described causing varying treatment results. Depending on the anatomical form, complete remission (CR) rates of up to 80–90% and remission durations of up to 22 months have been described.6–9 Most of the protocols however still consist of long-term maintenance chemotherapy. This – in comparison to the situation in the dog, in which discontinuous protocols have been shown to bear no outcome disadvantage to continuous treatment regimens – raises the question whether maintenance chemotherapy is necessary for long-time remission and survival in the cat or whether a maintenance-free protocol can achieve comparable results.10–14 Therefore, the aim of this study was to evaluate the outcome and toxicity of a short-term, maintenance-free combination chemotherapy protocol of 12-week duration for the treatment of feline high-/intermediate-grade lymphoma.

Materials and methods
Patients
Cats with a histologically or cytologically confirmed diagnosis of high-/intermediate-grade lymphoma based on the Working Formulation Classification system were eligible for this study. Cats with low-grade lymphoma were excluded from the study. Further eligibility criteria were no other serious
medical illness limiting full compliance with the study and signed owner consent.

**Pretreatment evaluation**

Pretreatment evaluation consisted of physical examination, complete blood count (CBC), serum biochemistry, FeLV and feline immunodeficiency virus (FIV) testing (FeLV Antigen/FIV Antibody Test Kit (SNAP® Kombi Plus FeLV Antigen/FIV Antikörper Test, IDEXX GmbH, Ludwigsburg, Germany]), urinalysis, thoracic and abdominal radiographs, abdominal ultrasound and bone marrow aspiration cytology, if indicated by abnormalities in the CBC, an electrocardiogram (ECG) and documentation of measurable disease. Tumours were measured either directly with callipers or via radiographic or ultrasonographic imaging. Clinical staging was performed following the modified clinical staging system for feline lymphoma.15

**Chemotherapy regimen and patient monitoring**

Patients were treated with a 12-week cyclic combination chemotherapy protocol consisting of L-asparaginase (Asparaginase 5000, −10 000 Medac®, Medac, Hamburg, Germany), vincristine [Vincristine sulphate (cellcristin®, cell pharm GmbH, Bad Vilbel, Germany]), cyclophosphamide (Endoxan®, Baxter Oncology, Frankfurt/Main, Germany), doxorubicin [Doxorubicin-HCl (Doxo-cell®, cell pharm GmbH)] and prednisolone (Prednisolon®, Jenapharm, Brehna, Germany) (Table 1). Dexamethasone (Dexamethason®, Jenapharm, Brehna, Germany) or prednisolone6 was applied before administration of L-asparaginase and doxorubicin.

Prior to each treatment CBC and serum biochemistry were performed. ECG and – if indicated – an echocardiographic examination were performed prior to each doxorubicin treatment. Tumour size was evaluated at each visit by direct measurement and radiographic or ultrasonographic imaging. In case of CR, treatment was stopped after the 12th treatment and cats were rechecked in 2- to 4-week intervals. Owners of cats with PR, SD or PD were offered cyclic combination maintenance chemotherapy or rescue chemotherapy. In case of relapse, patients were treated with a second cycle of chemotherapy either with the initial protocol or another combination treatment.

**Response assessment**

To evaluate response to therapy the following criteria were used: 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 all measurable disease; progressive disease (PD), >25% increase in size of all measurable disease or the appearance of new lesions. SD and PD were also classified as no response (NR). All responses and SD were required to last for at least 21 days.

**Assessment of toxicity**

Results of CBC as well as signs of gastrointestinal or other toxicity were recorded 1 week after each treatment. Adverse events were graded according to the Veterinary Co-Operative Oncology Group’s common terminology criteria for adverse events (VCOG-CTCAE).16 The number of neutropenic episodes as well as episodes of gastrointestinal (anorexia, diarrhoea and vomiting) or other

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**Table 1.** 12-Week chemotherapy protocol used for the treatment of lymphoma in 26 cats

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>l-Asparaginase</td>
<td>400 IU kg⁻¹ SC</td>
<td>•</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.025 mg kg⁻¹ IV</td>
<td>•</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>10 mg kg⁻¹ IV</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1 mg kg⁻¹ IV infusion</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>PO × 7 days (2 mg kg⁻¹) (1 mg kg⁻¹) (0.5 mg kg⁻¹)</td>
<td></td>
</tr>
</tbody>
</table>

•, drug administered.
Short-term chemotherapy in feline lymphoma

Twenty-six cats entered the study between November 2005 and July 2011. Breeds represented were Maine Coon (n = 2), Siamese (n = 2), Norwegian forest cat (n = 1), Exotic Shorthair (n = 1) and European Shorthair (n = 20). Median age was 6 months (range 2–33 months). Median body weight was 4.2 kg (range 0.9–10.2 kg). Median anatomic classification was Stage I or II (n = 23; 88.5%), Stage III (n = 3; 11.5%), and Stage IV (n = 0). Median clinical stage at diagnosis was Stage 2b (n = 12; 46.2%). Median duration of clinical signs before diagnosis was 3 months (range 1–20 months). Median number of treatment delays was 1 (range 0–3). Median number of treatment-related episodes of toxicosis (neutropenia, anorexia, vomiting, diarrhea) was 1 (range 0–6). The influence of the above patient factors on their independent influence on remission and survival times (1) patient variables (gender, age, body weight, anatomic classification, clinical stage, subclass, FIV/FeLV status, duration of clinical signs before diagnosis, corticosteroid pretreatment and presence of anaemia and thrombocytopenia at diagnosis) and (2) treatment-related variables (CR status (survival analysis only), treatment delay, duration of clinical signs before diagnosis, corticosteroid pretreatment, presence of anaemia and thrombocytopenia at diagnosis) was used to evaluate the patient factors with significance in the prior univariate analysis to be evaluated by multivariate Cox regression analysis. A P-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS 19 (IBM Deutschland GmbH, Ehningen, Germany). All statistical analyses were performed using SPSS 19 (IBM Deutschland GmbH, Ehningen, Germany).

### Results

#### Patient population

Twenty-six cats entered the study between November 2005 and July 2011. Breeds represented were Maine Coon (n = 2), Siamese (n = 2), Norwegian forest cat (n = 1), Exotic Shorthair (n = 1) and European Shorthair (n = 20). Median age was 6 months (range 2–33 months). Median body weight was 4.2 kg (range 0.9–10.2 kg). Median anatomic classification was Stage I or II (n = 23; 88.5%), Stage III (n = 3; 11.5%), and Stage IV (n = 0). Median clinical stage at diagnosis was Stage 2b (n = 12; 46.2%). Median duration of clinical signs before diagnosis was 3 months (range 1–20 months). Median number of treatment delays was 1 (range 0–3). Median number of treatment-related episodes of toxicosis (neutropenia, anorexia, vomiting, diarrhea) was 1 (range 0–6). The influence of the above patient factors on their independent influence on remission and survival times (1) patient variables (gender, age, body weight, anatomic classification, clinical stage, subclass, FIV/FeLV status, duration of clinical signs before diagnosis, corticosteroid pretreatment and presence of anaemia and thrombocytopenia at diagnosis) and (2) treatment-related variables (CR status (survival analysis only), treatment delay, duration of clinical signs before diagnosis, corticosteroid pretreatment, presence of anaemia and thrombocytopenia at diagnosis) was used to evaluate the patient factors with significance in the prior univariate analysis to be evaluated by multivariate Cox regression analysis. A P-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS 19 (IBM Deutschland GmbH, Ehningen, Germany). All statistical analyses were performed using SPSS 19 (IBM Deutschland GmbH, Ehningen, Germany).

#### Table 2. Adverse effects (AEs) in cats treated with multiagent short-term chemotherapy protocol, graded according to VCOG-CTCAE

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Total number of AE n (%)</th>
<th>Median number per cat (range)</th>
<th>VCOG grade (%)</th>
<th>AE after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>27 (12) 46 (0.5–6)</td>
<td></td>
<td>1 2 3 4 5</td>
<td>Vincristine/L-asparaginase Vincristine Cyclophosphamide Doxorubicin</td>
</tr>
<tr>
<td>Anorexia</td>
<td>41 (18) 75 (1.5–6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (10) 42 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3) 13 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>17 (12) 48 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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#### Toxicity (lethargy) during the treatment time were documented for each cat (Table 2).

### Statistical analysis

Complete remission (CR) and partial remission (PR) rates were defined as number of cats achieving CR or PR compared with the total number of cats treated. First remission duration was defined as the time from documentation of CR or PR to relapse. Kaplan–Meier product limit analysis was used for remission and survival analysis. A complete event was defined as lymphoma relapse (remission analysis) or death due to any cause (survival analysis). Cats were censored if they were alive at the time of data accrual closure (survival analysis) or were still in remission (remission analysis) at the time of data accrual closure. Kaplan–Meier Product Limit Analysis was used to evaluate the following variables for their independent influence on remission and survival times: (1) patient variables (gender, age, body weight, anatomic classification, clinical stage, subclass, FIV/FeLV status, duration of clinical signs before diagnosis, corticosteroid pretreatment and presence of anaemia and thrombocytopenia at diagnosis) and (2) treatment-related variables (CR status (survival analysis only), treatment delay, duration of clinical signs before diagnosis, corticosteroid pretreatment, presence of anaemia and thrombocytopenia at diagnosis) were included in the multivariate analysis. A P-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS 19 (IBM Deutschland GmbH, Ehningen, Germany). All statistical analyses were performed using SPSS 19 (IBM Deutschland GmbH, Ehningen, Germany).
7 years (range: 1–17 years). Median body weight was 4.6 kg (range: 2.6–8.1 kg). Fifteen cats were male (14 castrated male) and 11 cats were female (9 spayed female). Six cats (23%) had previously been treated with corticosteroids (in one case in combination with one dose of doxorubicin) and 20 cats (77%) had no prior treatment. Seventeen cats presented with inappetence, eight with vomiting, eight with lethargy and five with weight loss and four cats experienced dyspnoea. Median duration of clinical signs at presentation was 14 days (range: 2–120 days).

Clinical staging
Alimentary lymphoma was diagnosed in 10 cats, mediastinal lymphoma in 3 cats and 4 cats had multicentric lymphoma. The remaining nine cats had extranodal lymphoma, including renal (n = 2) and hepatic (n = 2) disease as well as lymphoma of the cervical subcutaneous tissue (n = 1), pharyngeal lymphoma (n = 1) and nasal lymphoma (n = 1). Three individuals (12%) were classified as stage 1, 3 (12%) as stage 2, 3 (12%) as stage 3, 14 (54%) as stage 4 and 3 cats (12%) as stage 5. Four cats (15%) were substage a and 22 (85%) substage b. Aspiration cytology of the bone marrow was performed in seven cats, two of which showed lymphoma involvement.

Laboratory parameters
At presentation 8 of 26 cats were anaemic with haematocrit (HCT) ranging between 11 and 26%. Median HCT in all patients was 32% (range: 11–42%). Thrombopenia was found in six individuals (range: 45 000–177 000 μL⁻¹; normal range: >200 000 μL⁻¹) with a median number of 304 000 thrombocytes μL⁻¹ in all cats. Neutropenia was diagnosed in one cat (1470 μL⁻¹, normal range: >2000). Three cats were presented with hypercalcaemia (ionized calcium concentrations: 1.44–1.51 mmol L⁻¹; normal range: 1.15–1.35 mmol L⁻¹).

FIV/FeLV status
One cat with intestinal lymphoma was FIV positive (4%). Six cats (23%) were FeLV positive (one alimentary lymphoma, two multicentric disease, one hepatic lymphoma and two mediastinal lymphoma).

Treatment response
Median time from diagnosis to induction chemotherapy was 2 days (range: 0–63 days). Median time from induction chemotherapy to documentation of remission was 8 days (range: 1–113 days). Response distribution in the 26 patients was as follows: CR: 12 (46%), PR: 7 (27%), SD: 4 (15%) and PD: 3 (12%). None of the variables analysed had a significant association with the likelihood for a cat to reach CR. At the time of data accrual closure four cats were alive at 289, 310, 1042 and 2229 days and 22 cats had died (19 because of lymphoma, 2 because of other causes and 1 because of unknown causes).

First remission duration
Twelve cats achieved a CR. Median CR duration was 394 days (range: 25–2116 days, 95% confidence interval: 25–2116 days, Fig. 1). In this subset of
Table 3. Outcome of 26 cats with lymphoma treated with a 12-week combination chemotherapy protocol grouped by anatomical type

<table>
<thead>
<tr>
<th>Anatomical type</th>
<th>n</th>
<th>Response pattern</th>
<th>CR duration</th>
<th>Survival duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimentary</td>
<td>10</td>
<td>CR: n = 4, PR: n = 2, SD: n = 2, PD: n = 2</td>
<td>Median: 1043 days (range: 35–2116 days)</td>
<td>CR cats: median: 1656 days (range: 1048–2230 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall: median: 78 days (range: 9–2230 days)</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>3</td>
<td>CR: n = 1, PR: n = 1, SD: n = 1, PD: n = 0</td>
<td>58 days</td>
<td>CR cat: 66 days, PR cat: 82 days, SD cat: 31 days</td>
</tr>
<tr>
<td>Multicentric</td>
<td>4</td>
<td>CR: n = 3, PR: n = 1, SD: n = 0, PD: n = 0</td>
<td>Median: 394 days (range: 28–394 days)</td>
<td>CR cats: median: 124 days (range: 62–454 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall: median: 62 days (range: 31–454 days)</td>
</tr>
<tr>
<td>Extranodal</td>
<td>9</td>
<td>CR: n = 4, PR: n = 3, SD: n = 1, PD: n = 1</td>
<td>Median: 235 days (range: 25–310 days)</td>
<td>CR cats: median: 251 days (range: 62–380 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall: median: 124 days (range: 22–380 days)</td>
</tr>
</tbody>
</table>

12 cats that achieved CR, univariate Cox regression analysis showed that of the analysed variables clinical stage ($P = 0.018$), pretreatment with corticosteroids ($P = 0.003$) and the presence of anaemia at diagnosis ($P = 0.013$) significantly influenced remission duration. Multivariate analysis showed that only the variable pretreatment with corticosteroids retained independent influence on CR duration ($P = 0.025$), with cats without pretreatment ($n = 10$) achieving a median remission duration of 1043 days (range: 28–2116 days), whereas cats with corticosteroid pretreatment ($n = 2$) had CR durations of 25 and 35 days.

In the seven cats with PR, remission duration ranged between 22 and 123 days (median: 41 days, 95% confidence interval: 13–69 days, Fig. 1). Remission outcome grouped by anatomical type of lymphoma is described in Table 3.

Survival

Median follow-up period for all cats and for cats with CR was 78 days (95% confidence interval: 20–136 days) and 232 days (95% confidence interval: 73–511 days), respectively.

In the 12 cats that achieved CR, median survival duration was 454 days (range: 62–2230 days, 95% confidence interval: 0–1490 days, Fig. 2).

While in the univariate regression analysis the variables anatomic classification ($P = 0.046$), thrombocytopenia $P = 0.039$) and total duration of treatment delay ($P = 0.032$) showed a significant effect on survival duration, none of these retained...
an independent significant influence on survival duration in the multivariate analysis. Survival times of those cats reaching PR only \( (n = 7) \) ranged from 31 to 174 days (median: 82 days, 95% confidence interval: 72–92 days) and survival duration of cats with SD \( (n = 4) \) and PD \( (n = 3) \) ranged from 9 to 48 days (median: 10 days) and 9 to 22 days (median: 17 days), respectively (Fig. 2).

Considering all 26 cats into account, overall survival amounted to 78 days (range: 9–2230 days, 95% confidence interval: 20–136 days). Multivariate regression analysis of patient- and treatment-related variables showed that presence of thrombocytopenia at diagnosis \( (P = 0.03) \) and failure to reach CR \( (P < 0.001) \) retained independent significant influence on outcome in exhibiting a negative association with survival duration. Survival outcome grouped by anatomical type of lymphoma is described in Table 3.

Toxicosis

Number of neutropenic episodes occurring in each cat during the 12-week treatment time ranged from 0 to 6. Of the cats experiencing neutropenia \( (n = 12, 46\%) \), a single neutropenic episode was found in four individuals, two episodes in four animals and three episodes in three animals, whereas one individual underwent six episodes of neutropenia. A total number of 27 neutropenic episodes were documented in the study population. Neutropenia was grade 1 in 44\% \( (n = 12) \), grade 2 in 41\% \( (n = 11) \), grade 3 in 11\% \( (n = 3) \) and grade 4 in 4\% \( (n = 1) \) of cases. Three (11\%) neutropenic episodes occurred after induction treatment with vincristine and L-asparaginase. The distribution of the remaining episodes of neutropenia was 14 (52\%) after treatment with vincristine, 7 (26\%) after treatment with cyclophosphamide and 3 (11\%) after treatment with doxorubicin (Table 2).

Altogether there were 28 treatment delays in the study population. In 23 of these cases (82\%), a delay of the subsequent treatment for 3–17 days (median: 5 days) was undertaken because of neutropenia. Treatment delay showed no statistical influence on outcome. Subsequent to four neutropenic episodes a dose reduction to 80% was undertaken in one cat.

Episodes of anorexia were documented 41 times in 18 cats (75\%) and 6 cats (25\%) had no signs of anorexia (median: 1.5; range: 0–6). The episodes of anorexia were grade 1 in 18 (44\%), grade 2 in 22 (54\%) and grade 3 in 1 (2\%) of the documented cases. Ten (24\%) episodes of anorexia arose after induction treatment (vincristine and L-asparaginase), 7 (17\%) after vincristine, 12 (29\%) after cyclophosphamide and 12 (29\%) after doxorubicin (Table 2).

Concerning the individuals’ weight development during the treatment and follow-up period it was documented that 14 cats (53.8\%) maintained their weight, 10 cats (38.5\%) experienced a weight reduction of >10% of their initial weight and two individuals (7.7\%) experienced a weight gain (>10%). Weight development did not exert a statistically significant influence on remission and survival times.

Discussion

As in human oncology, maintenance-free chemotherapy protocols in dogs have, in recent years, been shown to be effective and comparable to their long-term counterparts and are since established as standard treatment.\(^{10–14}\) By contrast in feline lymphoma, protocols containing long-term maintenance phases leading to varying results concerning outcome and tolerability are still the mainstay of treatment.\(^{5–8,17,18}\) First indications that also in cats with lymphoma, satisfactory outcome may be possible with a combination protocol lacking a maintenance phase were described recently in a study in which a subset of cats inadvertently did not receive maintenance chemotherapy because of owners’ decisions to discontinue treatment and in spite of this displayed long-term remission and survival.\(^{8}\)

This study in consequence aimed at prospectively investigating a combination chemotherapy protocol lacking maintenance treatment in cats with intermediate-/high-grade lymphoma. Results show that in the presented population of cats indeed long-term first remission and survival durations were attainable without maintenance chemotherapy. Those cats experiencing CR discontinued treatment after completion of the 12-week protocol...
and subsequently exhibited median remission and survival durations of 394 and 454 days, respectively.

Comparison of outcome results across studies is not possible without limitations arising through possible differences between institutions in, for example, staging procedures, patient selection and owner populations. Keeping these limitations in mind, however, the remission duration results attained with the presented discontinuous protocol are comparable to those of other previously reported continuous treatment regimens reporting, for example, median CR times of 281, 251, 264 and 421 days. In addition, the presented remission duration results compare favourably to the results attained in a feline lymphoma population treated with single-agent doxorubicin reporting a median CR duration of 92 days.

In comparison to remission time, survival duration is a less robust parameter in describing outcome because differences in clinician opinion and especially owners’ perceptions of their pet’s quality of life or even financial possibilities and in that their willingness to pursue further (rescue) treatments and the decision for time point of euthanasia can greatly impact the length of survival in the individual patient. Nonetheless, this parameter is of interest to the client and therefore represents meaningful data for the consulting clinicians. Bearing these aspects in mind, the survival duration attained in the cats experiencing CR in the presented population also may be considered satisfactory. Furthermore, survival is – considering the above mentioned limitations of an interinvestigational comparison – similar or even compares favourably to those results attained by previous investigations using longer term maintenance chemotherapy regimens.

These results show that as in dogs, maintenance chemotherapy may not be necessary to attain satisfactory outcome in feline lymphoma and that short-term combination chemotherapy protocols may represent a good alternative treatment. Lack of a maintenance therapy that is associated with continuous hospital visits allows for longer term treatment-free periods and in this has the potential to greatly improve the cats’ quality of life in addition to making treatment more feasible even for owners with financial or logistic restrictions.

However, it must also be mentioned that the favourable survival durations only apply to the subgroup of cats reaching CR. Less favourable survival times are found when looking at the group of treated cats as a whole, in consequence to the lower survival durations of individuals with PR, SD or PR. In these cases, the cats oftentimes were euthanized because of owner request before the completion of the chemotherapy protocol.

Prerequisite for long-term outcome was therefore for a cat to reach CR. The importance of achieving CR has been reported formerly. The fact that response, however, can only be assessed during and not before treatment limits its utility as a true prognostic factor. Furthermore, none of the parameters analysed in this study showed a significant association with the likelihood for a cat to reach CR. These aspects emphasize the need for future studies to identify indicators – potentially molecular and genetic markers – that allow for a prognostication concerning individual response before treatment is begun.

Despite the favourable remission and survival times in the group of cats with CR, the response rate in this study encompassing a CR rate of 46% must be considered as being unsatisfactory. Previous studies have indeed reported varying response results. On one hand, higher CR rates of 75, 74 and 62% have been described. In contrast, there are other studies reporting comparable results with CR rates of 52, 47, 43, 26 or 11–18%. This response pattern and the considerably short survival of cats with PR and SD consequentially lead to the short overall survival duration documented in the present group of cats as a whole.

Causes for the apparently low response rate in this study remain unclear. Epidemiologic characteristics of the 26 cats were largely comparable to the literature. The median age of 7 years is slightly below that of previous investigations; breed, gender and weight characteristics are in conformity to prior studies. In the current population, nearly one quarter of cats were tested FeLV positive, which falls slightly below the previous studies assessing ratios of 25–27%, however does exceed others reporting 0–15% of FeLV-positive cats. FeLV positivity has been described as a negative prognostic
parameter20,22 – to what extent the relatively high positive proportion plays a role in the low response rate of the current study however remains speculative, especially in face of this parameter not exhibiting any statistically detectable relevance.

Although not definitively provable, it is possible that an increased owners’ readiness to undergo chemotherapy because of the short and overseeable character of the protocol, even in cats in a worse condition to a certain degree, may have contributed to the less favourable response pattern. This however remains notional, although considering the clinical stages of the study population this presumption may be supported by the circumstance that a larger proportion of individuals were evaluated as stages 4 and 5 than in the previous study with higher CR rates.8 The similar distribution of substages as well as the lack of these parameters displaying statistical significance are on the other hand unsupportive in this context.

The chemotherapy protocol itself used in this study is nonetheless unlikely to account for the comparably low CR rate. The 12-week regimen is very similar to induction phase and following weeks of other combination protocols7,8,26 and the median time for a cat to reach remission amounted to 7 days; therefore, other factors must have contributed to the documented responses.

The most frequently encountered toxicosis in this study was anorexia, which was documented at least once in 75% of the study population. Although mostly low grade in the current patient population, loss of appetite may indeed represent a problem in the treatment of cats with lymphoma as it has the potential of worsening their medical condition and if present repeatedly may lead to significant weight loss. This is also reflected by the presented cat population in which 40% of the cats experienced some degree of weight loss during the course of their treatment. In this study, weight development during treatment had no influence on outcome. However, a negative association between weight loss before starting chemotherapy and the likelihood to achieve CR has previously been reported in cats.17 Additionally, two recent studies have shown the prognostic significance of baseline body weight and weight changes during the course of treatment of feline lymphoma.25,27 Exact reasons for the occurrence of anorexia not accompanied by vomiting in cats undergoing chemotherapy are difficult to elucidate; however, they may probably – as in humans – be associated with sustained nausea and with that considerably impact the individual’s quality of life. This observed frequency of anorexia, which has also been described previously,19,20,28 as well as its consequences on prognosis and quality of life emphasize the need to develop treatment strategies ameliorating this chemotherapy-related adverse effect and targeting weight loss.

Other gastrointestinal as well as the haematologic toxicoses in this study were mostly low grade, and in that were comparable to previous studies.7,19,20,23 However, it must find mentioning that the frequency of toxicoses in the study protocol was higher than in some previously reported regimes9 and treatment delays were a possible consequence. These treatment postponements were documented mostly in consequence to episodes of neutropenia. Unlike previous canine studies in which treatment delays have been shown to be associated with better outcome14,29 this neither had a negative nor positive impact on prognosis in the presented feline population. Additionally, no case was in need of hospitalization and only one cat experienced a dose reduction. In summary, therefore, the presented treatment regimen in addition to leading to satisfactory outcome may also be considered as a protocol with acceptable tolerability.

Limitations of this study must also find mentioning. Most importantly, the low number of patients accrued must indeed be seen as the major limiting factor. Therefore, for example, the value of prognostic variables must be interpreted with care as the number of individuals in the subgroups may have been too small to generate reliable evaluations. Furthermore, the external validity of a clinical trial is subject to limitations based on a number of factors such as selection bias and population differences.30 Factors contributing to reductions of external validity include patient characteristics, referral bias or even pet owner-related factors such as financial considerations influencing the decision for a certain treatment. The patient population presented may therefore not be representative for the feline lymphoma population in general, limiting
the external validity of the results of this study and restricting the results to the studied population. Additionally, because of the low number of patients the possibility of lack of power to detect significant differences especially when analysing the prognostic significance of variables must be considered. Furthermore, the study was not designed as a randomized, controlled investigation comparing to current established protocols. Therefore, decisive statements on the equality of the study protocol with long-term maintenance regimes cannot be finalized and investigations including higher patient numbers into two-arm, randomized evaluations of continuous and discontinuous protocols are warranted to more definitively clarify this important question in the treatment of feline lymphoma. The satisfactory outcome results as well as the good tolerability of the presented 12-week protocol may however serve as an encouraging support for the future performance of these investigations.

Conflict of interest

The authors declare that there is no conflicts of interest.

References

16. VCOG. Veterinary Co-operative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy.


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