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Evaluation of low-dose metronomic (LDM) cyclophosphamide toxicity in cats with malignant neoplasia

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Abstract

Oral administration of low-dose cyclophosphamide in pets with spontaneously occurring malignant neoplasms has become a common practice in veterinary medicine. The purpose of this retrospective study was to investigate toxicity events in cats with spontaneous malignancies receiving cyclophosphamide as a metronomic therapy for at least 1 month. The number and severity of clinical, haematological and biochemical adverse events were recorded according to the Veterinary Cooperative Oncology Group's Common Terminology Criteria for Adverse Events v1.1 classification scheme. Twenty-four cats were enrolled in the study with a total number of 27 neoplasms: 13 sarcomas, 12 carcinomas, one melanoma and one neuroendocrine tumour. Seventeen cats presented with macroscopic disease, while seven had microscopic disease. Seven cats (29%) had metastasis either to the regional lymph nodes and/or distant sites at the time of study enrolment. Additional medications, administered concurrently, included non-steroidal anti-inflammatory drugs (17), toceranib (4) and thalidomide (7). Four cats showed grade I gastrointestinal toxicity during the first month of treatment, which was controlled with antiemetics. Overall, 2/24 cats (8%) showed grade I haematological toxicities and 1/24 (4%) showed grade I renal toxicity in the first 4 weeks. Median follow-up for all cats was 30 days (range 30–360 days). For the 15 cats with follow-up longer than 1 month the only additional toxicities observed were two grade III and one grade II azotaemia that occurred after 2 months of therapy. Low-dose cyclophosphamide seems to be a well-tolerated option for cats bearing primary or metastatic tumours. Evaluation of toxicity after long-term administration is still needed.

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Introduction

Low-dose metronomic (LDM) chemotherapy therapy is defined as the chronic administration of low doses of cytotoxic drugs on a continuous or semi-continuous basis without resting pauses, not necessarily reflecting the drug's mechanism of action, but the interval and dose.[1] Cyclophosphamide is the most widely explored agent used in this way in human and veterinary medicine. The metronomic setting differs in anti-tumour effect mechanisms from conventional maximum tolerated dose (MTD) cytotoxic therapy. MTD therapy has a direct cytotoxic effect on proliferating, neoplastic and healthy cells and, although new blood vessel formation is affected by high-dose chemotherapy, the inter-administration intervals allow the endothelial cells to repopulate, vanishing the anti-angiogenic effect. In contrast, LDM chemotherapy mainly exerts its anticancer activity through anti-angiogenic activity and positive stimulation of the anti-tumour immunosurveillance system, mechanisms that can arrest tumour cell growth without causing adverse effects in normal tissues.[1]

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LDM chemotherapy can induce apoptosis of macro- and microvascular endothelial cells,[2] increase production of thrombospondin I[3] (an endogenous angiogenesis inhibitor), decrease release of circulating vascular endothelial growth factor (VEGF)[4,5] and decrease the number of circulating endothelial precursor cells (CEPs),[6,7] which are components of the tumour microenvironment and play a major role in enhancing angiogenesis. CEPs seem to have a specific sensitivity to continuous LDM chemotherapy, while, with an MTD schedule, gaps between drug administrations allow them to repopulate.

LDM chemotherapy in human and veterinary medicine is often combined with cyclo-oxygenase 2 (COX-2) inhibitors, thalidomide or tyrosine kinase inhibitors, with the goal of increasing anti-angiogenic potential.[8] COX-2 inhibitors have been demonstrated to exert an anti-angiogenic effect in cancer cells by blocking COX-2 receptors and stopping the intracellular signalling cascade that leads to production of growth factors such as VEGF, basic fibroblast growth factor and/or tumour growth factor (TGF)-β.[8] Tyrosine kinase inhibitors, such as toceranib, target and block signalling from VEGF and platelet-derived growth factor receptors.[9,10] Thalidomide possesses anti-inflammatory and immunomodulatory properties, which contribute to its anti-angiogenic effect. Specifically, thalidomide inhibits the synthesis of tumour necrosis factor-α in monocytes, microglia and Langerhans cells.[11]

LDM chemotherapy also decreases the number of circulating T regulatory cells (T-regs) and level of immunosuppressive cytokines such as TGF-β, interleukin (IL)-10 and IL-22, while enhancing the maturation of dendritic cells,[12] as shown in mouse models. Increased numbers of circulating T-regs have been demonstrated in humans with cancer[13] and in tumour-bearing dogs. Additionally, a decrease in blood circulating T-reg levels has been reported with continuous low-dose cyclophosphamide administration resulting in increased $CD8^+$ cytotoxic T cells, which are important effector cells in immune responses against tumour cells.[14]

LDM chemotherapy is an attractive therapeutic option because of its proposed low toxicity profile, low cost and ease of administration. Most LDM drugs are given orally and facilitate at-home therapy. In the past decade, LDM has gained popularity in veterinary oncology and has become a frequent option chosen by pet owners, despite the fact that a systematic evaluation of efficacy, systemic toxicity and established dosing protocols is lacking. LDM regimens evaluated in dogs have thus far included chlorambucil,[15] cyclophosphamide with or without etoposide,[14,16,17] or lomustine,[18] each of them in combination with COX inhibitors. These studies reported mild to moderate toxic events occurring in 14–50% of cases.[15–17] Overall, such protocols were considered to be safe and well tolerated, and also indicated an anticancer effect. Elmslie et al[16] showed a delay in tumour recurrence in dogs with microscopic soft tissue sarcomas treated with low-dose cyclophosphamide and non-steroidal anti-inflammatory drugs (NSAIDs) compared to historical controls. Lana et al[17] showed that LDM cyclophosphamide, etoposide and NSAIDs had a similar efficacy to MTD doxorubicin in dogs with resected splenic hemangiosarcoma. These results reinforce the notion that the anti-angiogenic properties of LDM chemotherapy represent a promising anticancer therapy in veterinary oncology. Encouraging results in dogs justify consideration of similar LDM therapy in cats, either when standardised intensive protocols are declined, as maintenance therapy after achieving tumour control with other local or systemic therapies, or as primary therapy to prevent or delay tumour growth while maintaining a good quality of life. In our experience, stress associated with repeated visits for injectable chemotherapy is a common reason cited by cat owners for declining or discontinuing traditional MTD treatment modalities, and oral LDM protocols could, potentially, be less stressful treatment for feline patients. To our knowledge, the current veterinary literature does not provide information about the prevalence of possible adverse effects or antitumour responses of LDM in cats. The potential positive features of this therapy warrant documentation of LDM chemotherapy safety and efficacy in tumour-bearing cats. The aim of this retrospective study was to evaluate the short- and long-term toxicity of metronomic regimens, including LDM cyclophosphamide in cats with malignant neoplasia.

Materials and methods

This study included cats presented for treatment of spontaneous malignant neoplasms treated with LDM cyclophosphamide at four different institutions (Royal Veterinary College, UK; Veterinary Teaching Hospital, University of Cardenal Herrera CEU, Valencia, Spain; Veterinary Faculty, Complutense University, Madrid, Spain; Animal Oncology and Imaging Center, Switzerland) between 2010 and 2013.

Patient selection

Diagnosis of malignant neoplasia was based on cytology or histopathology. Inclusion criteria consisted of treatment with LDM cyclophosphamide at least twice a week, a minimum follow-up period of 1 month after starting treatment, and available information regarding treatment regimen, adverse effect monitoring, toxicity and outcome. Patients that received MTD cytotoxic protocols prior to the start of LDM chemotherapy (completed set number of cycles or failed MTD therapy) could be included if a minimum time of 1 week had elapsed after the last dose of MTD cytotoxic therapy, and they

had a baseline complete blood count (CBC) and biochemistry profile prior to starting LDM therapy.

Recorded data

Cyclophosphamide dose and frequency of administration were recorded along with any other drugs included in the metronomic protocol. The Veterinary Co-operative Oncology Group's (VCOG) Common Terminology Criteria for Adverse Events version 1.1[19] were used to assess and grade gastrointestinal, haematological, renal or other toxicities. Information regarding the frequency and type of monitoring was recorded.

Information about tumour types, treatments prior to the start of LDM cyclophosphamide and stage of disease at time of starting therapy was recorded.

Cats receiving LDM chemotherapy were divided into two groups: those receiving LDM as an adjuvant treatment after having completed other therapies (surgery, radiation therapy and cytotoxic chemotherapy), named the 'adjuvant group', and those who received LDM cyclophosphamide as palliative treatment for advanced neoplasia after failing other therapies or when the clients declined up-front conventional options, named the 'palliative group'.

Owing to the heterogeneity of the patient study group regarding tumour types, stage and treatments previously received, an objective assessment of overall anticancer efficacy was not attempted. However, descriptive outcome information was gathered and when it was possible to assess a response, response evaluation criteria in solid tumours (RECIST) criteria were applied,[19] where complete response (CR) is defined as disappearance of all target lesions; partial response (PR) is defined as at least 30% reduction in the sum of diameters of target lesions, taking as reference the baseline sum; stable disease (SD) is defined as <30% reduction (PR) or 20% increase (progressive disease [PD]) in the sum of diameters of target lesions, taking as reference the smallest sum of diameters while on study. In our study, SD was considered if the subject did not show any PD for a minimum of 4 weeks from the treatment start; PD is defined either as the appearance of one or more new lesions or at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. Progression-free survival (PFS) was defined and recorded according to the VCOG consensus evaluation criteria guidelines[20] as the length of time during and after treatment in which a patient is living with a disease that does not meet the criteria for PD. Descriptive statistics, including median and range, were reported for all outcome variables evaluated using Microsoft Excel.

Results

Study group description

Twenty-four cats met the inclusion criteria. Details of signalment, tumour type and LDM regimen are shown in Table 1. The majority of cats were domestic shorthair (18), followed by Maine Coon (2), and domestic longhair (1), Persian (1), Egyptian (1) and Siamese (1). The median age was 11.7 years (range 7.0–19.0 years); median body weight was 4.3 kg (range 2.43–8.70 kg). Fourteen cats were female and 10 cats were male. All cats were neutered.

Tumour description

Twenty-two cats had one malignant neoplasm, and two cats had two and three different tumour types, respectively. The most common tumour type was sarcoma (13), followed by carcinoma (12), melanoma (1) and neuroendocrine tumour (1). Of the cats with multiple tumours, one had a history of injection site sarcoma (ISS) treated with surgery followed by hepatocellular carcinoma and the other presented with simultaneous colangiocarcinoma, thyroid carcinoma and ISS.

The palliative group included 17 cats with macroscopic disease and the adjuvant group had seven cats with microscopic disease.

In the palliative group, 16 cats had gross disease at the primary site and seven had metastatic disease, four with regional lymph node involvement and six with metastasis to distant organs. Previous failed therapies included cytotoxic chemotherapy (four cats), surgery (three cats) and photodynamic therapy (one cat).

In the adjuvant group, cats were previously treated with surgery, radiation therapy, cytotoxic chemotherapy or some combination of the three, with the intent of achieving an adequate local control of the primary tumour; therefore, they had no measurable disease. Specifically, 11 cats had previous surgery, three cats completed either a curative or palliative intent radiation course, and six cats received cytotoxic chemotherapy, including high-dose carboplatin (2), doxorubicin (4) with or without cyclophosphamide (2) and gemcitabine (2).

Treatment description

Cyclophosphamide was compounded in capsules of 5 mg, 10 mg, 25 mg or commercially available 50 mg tablets. Thirteen cats received cyclophosphamide every other day (EOD), 10 cats received it once daily, one cat twice weekly and one cat five times a week. The median dose was 14 mg/m^2 per administration (range 6–27 mg/m^2). The median total dose of cyclophosphamide per week was 66 mg/m^2 (range 25–140 mg/m^2).

Four cats received cyclophosphamide as monotherapy. Twenty cats received concurrent NSAIDs and/or toceranib and/or thalidomide (see Table 1): 17 cats had concurrent NSAIDs (11 cats received meloxicam at 0.05 mg/kg daily or EOD; six cats received piroxicam at 0.3 mg/kg daily or EOD; one cat received firocoxib at 1 mg/kg EOD; four cats received concurrent toceranib

Table 1 Description of the patient selection

Patient	Breed	Age (years)	Sex	Body weight (kg)	Tumour type	CYC schedule	CYC dose (mg/m^2)	Primary tumour	Metastasis	Additional drugs
1	DSH	11	FN	4.30	Injection site sarcoma	q24h	10.0	Microscopic	No	None
2	DSH	10	FN	3.44	Hemangiosarcoma (subcutaneous)	Twice weekly	21.0	Microscopic	No	Meloxicam
3	DLH	7	MN	4.75	Injection site sarcoma	EOD	17.0	Macroscopic	LN	Toceranib + meloxicam
4	DSH	9	MN	6.50	Injection site sarcoma	EOD	14.0	Microscopic	No	Meloxicam
5	DSH	8	MN	4.20	Angioleiomyosarcoma	EOD	19.0	Microscopic	No	Toceranib + meloxicam
6	DSH	9	FN	4.60	Injection site sarcoma	EOD	16.0	Microscopic	No	Toceranib + meloxicam
7	DSH	18	MN	5.80	Injection site sarcoma	q24h	15.0	Microscopic	No	Meloxicam
8	Egyptian	12	FN	3.70	Injection site sarcoma	EOD	10.0	Macroscopic	No	Thalidomide
9	DSH	14	FN	2.75	Oral fibrosarcoma	q24h	10.0	Macroscopic	No	Meloxicam
10	Siamese	8	MN	5.00	Oral fibrosarcoma	EOD	8.5	Macroscopic	No	Piroxicam
11	Maine Coon	7	MN	8.70	Hemangiosarcoma (subcutaneous)	EOD	6.0	Macroscopic	No	Thalidomide + piroxicam
12	Maine Coon	13	MN	6.20	Injection site sarcoma + hepatocellular carcinoma	q24h	15.0	Macroscopic	No	None
13	DSH	14	FN	4.50	Injection site sarcoma + cholangiocarcinoma + thyroid carcinoma	EOD	9.0	Macroscopic	Liver	Thalidomide + piroxicam
14	DSH	8	FN	4.10	Nasal squamous cell carcinoma	q24h	15.0	Macroscopic	No	Meloxicam
15	DSH	16	FN	4.50	Nasal carcinoma	q24h	10.0	Microscopic	No	Firocoxib
16	DSH	10	FN	3.60	Nasal squamous cell carcinoma	q24h	15.0	Macroscopic	No	Meloxicam
17	DSH	19	MN	4.10	Unknown origin carcinoma	EOD	10.0	Not assessable	Lungs	None
18	DSH	12	FN	2.90	Hepatocellular carcinoma	EOD	12.5	Macroscopic	Regional LN pancreas	Thalidomide + piroxicam
19	DSH	15	FN	2.90	Oral squamous cell carcinoma	q24h	15.0	Macroscopic	No	None
20	Persian	14	MN	3.00	Renal carcinoma	EOD	12.0	Macroscopic	LN	Thalidomide + piroxicam
21	DSH	12	FN	4.50	Mammary carcinoma	q24h	15.0	Macroscopic	No	Meloxicam
22	DSH	16	FN	2.43	Pancreatic adenocarcinoma	EOD	27.0	Macroscopic	LN and lungs	Toceranib
23	DSH	11	MN	5.50	Neuroendocrine tumour	EOD	8.0	Macroscopic	Lungs	Thalidomide + piroxicam
24	DSH	9	FN	3.21	Melanoma	5 times a week	20.0	Macroscopic	LN and lungs	Meloxicam

CYC = cyclophosphamide; DSH = domestic shorthair; DLH = domestic longhair; F = female; N = neutered; M = male; EOD = every other day; LN = lymph nodes

(2.5 mg/kg three times a week); six cats received thalidomide (5 mg per cat daily).

Baseline laboratory parameters prior to starting the LDM protocol were available for eight cats and included haematology, biochemistry and urinalysis values, all of which were within normal limits. No baseline laboratory values were available for the rest of the cats. CBC and biochemistry profiles were available for all cats after 1 month of LDM therapy. Fifteen cats had a follow-up period exceeding 1 month. In this group, bloodwork re-evaluations were performed monthly for two additional months and then sporadically at discretion of the attending clinician.

Adverse effects during the first 4 weeks

The incidence of toxic events assessed after 4 weeks of therapy was 29% and they were defined as mild to moderate in intensity. Specific toxicities are detailed as follows.

Gastrointestinal adverse effects. Overall, 4/24 cats (16%) had gastrointestinal adverse effects, considered mild to moderate (grades I to II), within 4 weeks of starting the metronomic treatment. The gastrointestinal adverse effects were anorexia, vomiting and diarrhoea. All of these cats were receiving concurrent meloxicam.

After 1 week of treatment, one cat showed decreased appetite (grade I anorexia) that resolved within a few days, without supportive treatment. Vomiting was observed in two cats: vomiting was resolved in one of the cats within a week without supportive treatment, while the other required two doses of injectable maropitant and a 5 day drug holiday from LDM cyclophosphamide therapy. Upon re-introduction of the therapy in this cat, no further vomiting occurred. Both vomiting cats were treated with concurrent cyclophosphamide and NSAIDs. One patient treated with LDM cyclophosphamide and toceranib had episodes of diarrhoea and soft stools after initiating the therapy (grade I); as such, it was not possible to establish which medication was responsible. The diarrhoea resolved with a course of metronidazole.

Haematological adverse effects. Two of 24 cats (8%) were reported to have haematological toxicity. One patient experienced mildly regenerative anaemia (grade II packed cell volume 22%). This cat concurrently received NSAIDs. Another patient, that previously received combination doxorubicin and carboplatin, was thrombocytopenic (grade I).

Other adverse effects. One cat of 24 (4%) was reported to have renal toxicity (grade I). This patient had normal renal values on presentation, but no previously recorded urinalysis. One month after starting LDM therapy (cyclophosphamide and toceranib) the urine was poorly concentrated (urine specific gravity [USG] 1.020; range for normohydrated patient 1.035–1.060) with normal blood urea and creatinine levels. This patient received concurrent toceranib.

Long-term adverse effects

Fifteen cats had a follow-up time >4 weeks (total follow-up median 207 days, range 60–420 days). There was no additional reported gastrointestinal toxicity during this extended period beyond the initial 4 weeks.

Renal toxicity was described in 3/15 cats (20%) and it was classified as moderate with grade II (1) and grade III (2). Among those patients, one cat's serum biochemistry profile showed mildly increased urea (grade I metabolic adverse effects) and normal creatinine 2 months after starting the LDM therapy. This cat had concurrent moderate to marked neutrophilia (33.8 × 10^9/l; reference interval 2.5–12.5 × 10^9/l) and a moderate non-regenerative anaemia (grade II). Five months later, the uraemia progressed to grade II and the creatinine was elevated at 299 µmol/l (reference interval 74.50–185.30 µmol/l; grade III). Urine sediment, culture and USG were not performed. This patient received a combination of cyclophosphamide and NSAIDs throughout.

Another cat had creatinine value that rose from 114 mmol/l to 203 mmol/l (grade II) after 2 months of treatment, which prompted the referring veterinarian to stop the treatment. No USG was performed. This patient also received a combination of cyclophosphamide and NSAIDs.

The single case with renal toxicity observed in short-term follow-up was observed to progress during the long-term monitoring. After 2 months of LDM cyclophosphamide and toceranib, this patient developed elevated urea. Continued monitoring identified stable urea and USG values at the 3 month evaluation; however, the creatinine level was increased (grade III). At the 6 month evaluation this patient's renal parameters had stabilised. This cat received a combination of cyclophosphamide and toceranib throughout.

Clinical signs of haemorrhagic cystitis were not observed in any cats for which long-term monitoring was available.

Tumour responses. PFS was calculated for both groups. The median PFS for the adjuvant group was 297 days (range 190–420 days), while in the palliative group it was 90 days (range 14–240 days).

Tumour response was assessed in the palliative group: none of the cats had CR, one cat had PR, 14 cats had SD, and two cats had PD.

Discussion

In humans, mainly because of their anti-angiogenic properties, LDM protocols are often elected for

advanced-stage cancer patients with the intent of stabilising disease without producing co-morbidity. In veterinary oncology, quality of life is the main goal above life expectancy. One advantage of LDM chemotherapy is the ease of administration: the protocols described herein were given orally at home. This route is particularly attractive, sparing cats the stress of travel, frequent clinic appointments, intravenous catheter placements, drug injections and potential undesirable adverse effects of MTD cytotoxic therapy. LDM chemotherapy could represent an attractive 'cat-friendly' alternative to more intense MDT treatments.

Studies in dogs[14–17] have already demonstrated that LDM protocols are well tolerated, with few mild-to-moderate adverse effects. The present retrospective study provides information about the tolerability and prevalence of adverse effects of LDM cyclophosphamide in cats with cancer. Based on our results, we can assert that low-dose cyclophosphamide protocols are well tolerated in cats with minimal numbers of toxic incidents occurring over the time period assessed, and adverse events were only mild to moderate in nature. These results are encouraging, and warrant further studies of efficacy in specific types of feline neoplasia.

The frequency of cats showing gastrointestinal toxicity was low (16%). Decreases in appetite or vomiting seemed to be transitory episodes occurring during the first 4 weeks of treatment, and were self-limiting or readily controlled by antiemetic drugs. One cat showed diarrhoea (grade I), but this was one of the patients receiving toceranib together with cyclophosphamide. Toceranib is known to potentially cause diarrhoea in dogs;[21] therefore, it is difficult to assess whether the cause of the diarrhoea for this cat was the low-dose cyclophosphamide or toceranib. Moreover, it is important to consider that all cats with gastrointestinal toxicity were treated simultaneously with meloxicam, which, in a previous study, has been reported to have gastrointestinal adverse effects in about 4% of cases.[22] No further gastrointestinal adverse effects were recorded in the group of cats with longer follow-up (beyond 4 weeks). Often, gastrointestinal toxicity is perceived by the owners as strongly affecting their pet's quality of life; thus, our results support the use of LDM cyclophosphamide in cats, having low frequency and severity of gastrointestinal adverse effects within the first 4 weeks of treatment, and none afterwards.

The haematological adverse events reported at 4 week follow-up were mild and occurred in only 8% of the total population, with one recorded grade I thrombocytopenia and one grade II anaemia in patients with normal haematology values at baseline. While the reported thrombocytopenia may represent an effect of the LDM cyclophosphamide, it is important to consider that this may simply reflect a delayed adverse effect of prior therapy in this patient (doxorubicin and carboplatin). Importantly, resolution of thrombocytopenia was observed within 2 weeks, despite continued LDM cyclophosphamide therapy, potentially supporting the delayed adverse effect hypothesis. Additionally, given the relative inaccuracy of automated platelet counts in cats, this result may also reflect spurious error of automaticity, as no blood smear was reviewed.

A single grade II anaemia was observed in the 15 cats with longer follow-up, and was observed in a cat that experienced renal failure. Although, LDM cyclophosphamide-associated anaemia cannot be ruled out, the effects of renal disease on red blood cell numbers must be considered. This observation is important because it suggests that cats receiving LDM cyclophosphamide might not require frequent blood re-evaluations and this may further reduce the stress of therapy by limiting re-evaluation appointments involving venepuncture; however, only a limited number of cats had long-term follow up, so this statement requires further validation. LDM cyclophosphamide has been associated with renal toxicity in 6% of dogs in one study;[16] however, this was attributed to concomitant NSAIDs use and not directly to cyclophosphamide. Interestingly, three of our patients became azotaemic, despite the fact that they presented with baseline values within normal limits. During the first 4 weeks of treatment, only one cat of 24 (4%) showed renal toxicity grade I that progressed to grade III after 2 months of treatment. Unfortunately, a baseline for USG was not available for this cat, which received concurrent cyclophosphamide and toceranib. In a study by London et al,[21] 13% of dogs treated with toceranib developed elevated creatinine. A more recent study[23] on the use of masitinib (another tyrosine kinase inhibitor) in healthy cats showed reversible proteinuria in 10% of the population, with increases in serum creatinine concentration noticed over the 4 week period of treatment. In this study however, proteinuria was not assessed. These previous findings suggest that our patient could have suffered renal toxicity because of toceranib therapy, cyclophosphamide treatment or the combination of both.

In the group of 15 cats with longer follow-up, renal toxicity was recorded in two additional cats, and it was classified as moderate. Among these patients, one cat had neutrophilia concurrent with azotaemia. Unfortunately, urine sediment culture and USG were not performed and therefore it was not possible to rule out an infectious aetiology. The azotaemia did not resolve in the following months, despite the empirical use of antibiotics, and remained stable, ultimately classified as grade III renal toxicity.

Although renal toxicity secondary to LDM cyclophosphamide must be considered for these patients, it is important to remember they were also receiving NSAIDs.

Continuous use of meloxicam in cats could raise the suspicion of it being the cause of chronic renal failure progression; however, recent studies have demonstrated that COX inhibitors may not play a role in azotaemia progression.[24,25] Investigations into the renal impact of concurrent cyclophosphamide and meloxicam in cats have not yet been performed. Another reason to consider in the elevation of renal parameters is the possibility of renal metastasis, as two of these cats had advanced disease.

In total, the prevalence of nephrotoxicity reported in this study is low, with a percentage rising from 4% at 4 weeks to 12% after 2 months of treatment. Although we acknowledge the limitations in the renal toxicity evaluation in this study, it is possible that chronic use of cyclophosphamide can have an effect on the development of renal toxicity in cats treated with metronomic therapy – similar to what has been observed in dogs. This study is the first one to report this potential adverse effect of LDM in cats. Future studies to assess renal toxicity in cats on low-dose cyclophosphamide as a sole drug may be warranted.

Adverse effects of LDM cyclophosphamide described in dogs include sterile haemorrhagic cystitis (SHC), which is observed in about 9% of cases owing to the irritant effect of the metabolite acrolein on the urothelium of the bladder.[26] We did not record any episodes of SHC in our study population. This is, perhaps, to be expected: in fact, SHC is seldom seen in cats receiving higher-dose protocols,[27] meaning that a relative species-specific resistance to this adverse effect could exist.

Regarding patient outcome, the PFS data have to be considered in a critical way owing to the lack of previous treatment homogeneity and variety of tumours present carrying different biological behaviours. The median PFS of the adjuvant group was 297 days; in the palliative group it was 90 days. This likely reflects the fact that the palliative group had a large burden of disease and advanced clinical stages compared with the adjuvant group. Within a given group, the biological behaviour of different diseases likely dictated the differences in PFS (eg, progressive disease of 14 days for one cat with metastatic high-grade renal carcinoma, compared with a PFS of 240 days for a cat with a low-grade cutaneous hemangiosarcoma). In the palliative group, disease remained stable for 14 patients for at least 30 days. Interestingly, the only cat that showed subjective partial response was the one presented for an advanced neuroendocrine tumour, originating from the pancreas. That cat had a reduction in size of the pulmonary metastasis and improvement of the clinical signs, which lasted for 150 days. This cat received a combination of cyclophosphamide and thalidomide, without NSAIDs. However, conclusions cannot be made for either group regarding response evaluation, even if there is a difference in time to progression when LDM cyclophosphamide was used in the adjuvant setting.

This study has several limitations, the main ones being the small number of cats included and the lack of a standardised monitoring of adverse effects given the retrospective nature. The retrospective data could have led to recall bias and incompleteness of records when owners and referring veterinarians were contacted. Owing to the fact that many cats were end-stage patients, full staging was often not performed making it difficult to distinguish between true LDM chemotherapy adverse effects or complications due to the tumour progression. Also, a more homogeneous treatment regimen, in terms of dose, frequency of administration and concurrent drug(s), would have been ideal. To overcome these limitations, future prospective studies with planned monitoring and data collection of adverse effects, full staging and consistent follow-up are needed. Also, to assess for effectiveness of LDM, studies including only similar types of neoplasia should be performed.

Conclusions

LDM cyclophosphamide might have potential in providing cats with advanced neoplastic disease a good quality of life through a stress-free anticancer therapy while delaying tumour progression or recurrence, or even serve as a suitable alternative to some currently used MTD cytotoxic regimens. Our study reports that LDM cyclophosphamide has a low prevalence of toxicity, the most common adverse effects being mild and transient gastrointestinal signs and renal toxicity. This study provides evidence that LDM cyclophosphamide is safe in cats with cancer and further studies should be designed and implemented to assess its anticancer effect for specific tumour types, as well as prospective evaluation of long-term toxicity.

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