Clinical evaluation of the effectiveness of meloxivet in the complex treatment of cats with mammary gland carcinoma

D. Bilyi and M. Herhaulov*

Abstract

This study presents the results of a clinical administration of meloxivet nonsteroidal anti-inflammatory treatment against the background of the docetaxel + cyclophosphamide regimen chemotherapy following bilateral mastectomy in cats with mammary gland carcinoma. The inclusion of meloxivet in complex chemotherapy against breast carcinomas bilateral mastectomy improved treatment results. In particular, survival was extended in the clinical stages: I and II - by 1.3 times, III - by 1.6 times, and the disease-free period was increased by 1.5, 1.4 and 1.9 times, respectively. Complex treatment of cats including non-steroidal anti-inflammatory therapy reduced the risk of disease progression depending on the clinical stage during the first six months after the end of the course. An increase in the number of patients with subsequent metastasis (after six to twelve months) was also noted. The use of meloxivet made it possible to avoid disease progression in cats up to three years of age, and to reduce its probability and delay the onset of metastasis in all age categories. The proposed scheme of treatment of cats with mammary gland carcinomas reduced side effects, indicating an insignificant risk of negative effects of long-term meloxivet use against the background of a 1.5-fold reduction in the frequency of recurrences in the surgical intervention area.

Key words: *Cats; Tumours; Mammary gland; Non-steroidal anti-inflammatory drugs; Chemotherapy; Mastectomy*

Introduction

Mammary gland tumours are the third most common type of neoplasia in domestic cats (*Felis catus*) after skin and lymphohematopoietic neoplasms. Since they are characterised by a high risk of metastasis, and distant foci are present at the time of diagnosis, surgical intervention does not provide a cure. Meanwhile, patient owners are increasingly demanding the use of the most modern therapeutic means to improve the survival rate and quality of life of their companion animals (Giménez et al., 2010).

A high proportion of malignant types of mammary neoplasms in cats necessitates the use of chemotherapeutic protocols following mastectomy. Mauldin et al. (1988) presented the results of using

Dmytro BILYI*, DVM, Professor, (Corresponding author, e-mail: dmdmbeliy@ukr.net), Maksym HERHAULOV, Postgraduate, Faculty of Veterinary Medicine, Dnipro State Agrarian and Economic University, Dnipro, Ukraine

doxorubicin and cyclophosphamide for malignant non-hemopoietic tumours in cats. Of the 14 inoperable mammary gland tumours, seven cats showed a partial response to treatment, while seven had no response. Toxic effects were short-lived and did not require protocol change.

A progressive increase in serum creatinine concentration compared to the initial level due to neutropenia or anemia was found in cats treated with doxorubicin. Patients using doxorubicin monotherapy have a higher risk of serum creatinine elevation ≥0.3 mg/dL, compared to its inclusion in the CHOP-based chemotherapy protocol (odds ratio (OR): 20.0, 95% confidence interval (CI): 2.9–100). The average period before the increase in serum creatinine concentration was 119.3±89.7 days (Kopecny et al., 2020).

Considering chemoresistance, in order to increase the effectiveness of treatment, some studies have confirmed the feasibility of including salinomycin in treatment protocols in cats, as it can potentiate (C10 cells) or act synergistically (SCCF1 cells) with doxorubicin in certain feline cancer cells (sarcomas, carcinomas) (Borlle et al., 2019).

McNeill et al. (2009) found no benefit from adjuvant doxorubicin chemotherapy in cats with mammary carcinoma. The median progression-free period and overall survival in cats after mastectomy and on the background of the combination of chemotherapy with doxorubicin and surgical treatment were not significantly different and were 372 and 676 (P=0.15) and 1406 and 848 (P=0.78) days, respectively. However, overall survival in animals after unilateral mastectomy and adjuvant chemotherapy was significantly longer compared to mastectomy alone: 1998 *vs.* 414 days (P=0.03).

Despite the potential side effects of doxorubicin in cats (renal damage, myelosuppression, anorexia, and weight loss), Reiman et al. (2008) did not find an increase in its toxicity with an increase in the dose from 1 to 25 mg/m^2, except for a dynamic decrease in the number of neutrophils (P<0.001).

Cunha et al. (2017) indicated a benefit of mastectomy over adjuvant mitoxantrone or doxorubicin chemotherapy in cats with mammary carcinomas. After surgery, mean and median survival times were 1625 and 2404 days, the disease-free period was 815 days, while the chemotherapy protocol was 719, 690, and 549 days, respectively.

Toxicity, manifested by neuropenia, limits the dose of cyclophosphamide to 200–300 mg/m^2, the lowest in the period from 7 to 21 days of chemotherapy. Higher doses are considered safe when used in combination with prednisone and L-asparaginase (Chan et al., 2020). A safe use of cyclophosphamide at a dose of 460 mg/m^2 intravenously in combination with prednisone and L-asparaginase every 3 weeks is possible in cats with normal renal function (Moore et al., 2018).

Doublet therapy with gemcitabine (2 mg/kg intravenously) and carboplatin (10 mg/kg intravenously) has been reported to be well tolerated in cats with carcinomas. Toxic effects of this protocol included: grade 3 or 4 neutropenia (33.3%), grade 4 thrombocytopenia (16.7%), and grade 3 gastrointestinal toxicity (16.7%) (Martinez-Ruzafa et al., 2009).

Feline mammary carcinomas (FMCs) are characterised by high biological aggressiveness and a poor prognosis, with significant similarities to the corresponding human disease, including multidrug resistance mechanisms. The potential existence of chemotherapy resistance mechanisms in FMC is indicated by the simultaneous expression of proteins such as permeability glycoprotein (P-gp), lung

resistance protein, and metallothionein. At the same time, P-gp was expressed in 93.4% of FMC and was positively associated with tumour grade (P=0.049). metallothionein expression was significant in triple-negative basal- and normal-like molecular FMC subtypes (P=0.023) (Manoel et al., 2021).

Vascular endothelial growth factor, a key factor in the rapid progression and metastasis of mammary carcinomas in cats, is a potential therapeutic target. Using a cat mammary gland carcinoma xenograft model, Michishita et al. (2016) showed the ability of a single bevacizumab therapy to suppress tumour growth by inhibiting angiogenesis and increasing apoptosis.

Cyclooxygenase-2 expression level, along with histological grade and HER2 hormonal status, have a direct impact on overall disease prognosis. In particular, cyclooxygenase-2 immunoreactivity was higher in metastases than in primary tumours (P=0.007) and correlated with survival (P=0.089) (De Campos et al., 2016).

The general data supports the conclusion that the antitumour effect of nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase *in vivo* is determined and depends on the inhibition of tumour enzymes, primarily cyclooxygenase-2. The cellular effects observed when high concentrations of NSAIDs are added to tumour cells cultured *in vitro* may not be relevant to the mechanisms that mediate the effects of NSAIDs *in vivo* (Raz, 2002).

Currently, the general information highlights the significant role of cyclooxygenase (COX)-1 and -2 isoforms in the pathogenesis of oncological diseases, including mammary gland cancer in dogs and cats. However, the expression of cyclooxygenase-1 and -2 shows high immunohistochemical heterogeneity, which justifies the need for its further study (Gregório et al., 2021).

Malignant neoplasias, particularly feline mammary carcinomas are locally invasive and highly metastatic tumours. Their high metastatic potential requires the administration of chemotherapy after the removal of breast neoplasms, though currently, insufficient data are provided to evaluate the effect of such protocols.

For the oncological pathology of cats, in particular, neoplasia of the mammary gland, a large number of chemotherapeutic drugs have been clinically tested. However, the efficacy of most chemotherapeutic protocols remains controversial. Therefore, the development of more effective treatment regimens for cats with mammary gland malignancies remains relevant.

The purpose of this study was to study the clinical effectiveness of meloxivet against the background of mastectomy and chemotherapy with docetaxel and cyclophosphamide in cats with mammary gland carcinomas.

Materials and methods

The study was conducted in the setting of veterinary medicine hospitals: Vetservice private clinic, and state-owned clinics of the Shevchenkivskyi and Soborni districts of the city of Dnipro, Ukraine, as well as at the Department of Veterinary Surgery and Reproductive Medicine of the Dnipro State Agrarian and Economic University, Ukraine. The research period was 2020–2023.

At the stage of initial reception of cats with cancer, anamnestic data analysis, risk factors for each patient and clinical status were determined, and an assessment of their quality of life performed.

Determining the general condition of cats was combined with a study of

the clinical features of neoplastic lesions: multiplicity, size, relation to surrounding tissues, presence of necrotic areas. The time of the initial registration of the tumour by the owner (or a veterinarian), the dynamics of the disease development, etc. were also taken into account.

For the experiment, two groups of animals were formed, control and experimental (Table 1) of patients with mammary carcinoma aged 2 to 17 years. According to the TNM clinical classification (Owen, 1980; Cassali et al., 2018), they were verified as: stage I (T_1 N_0 M_0), stage II (T_2 N_0 M_0), or stage III (T_{1-2} N_1 M_0; T_3 N_{0-1} M_0).

In cats of both groups, high-frequency (high-frequency electrosurgical apparatus EHVCH-120-RH "Nadia-4") bilateral mastectomy with simultaneous removal of regional lymph nodes was performed according to the generally accepted technique.

The choice of the treatment protocol was based on the literature and practical data on the clinical use of various chemotherapeutic agents for mammary tumours in cats. The effectiveness of the drugs and the risk of effects when using them were also taken into account. The DC regimen (docetaxel+cyclophosphamide), which is recommended for breast cancer in human medicine, was chosen as the main chemotherapy protocol.

The possibility of long-term use of NSAIDs containing the active ingredient meloxicam in cats for mammary gland tumours is based on the published data of a number of researchers. The clinical effectiveness and minor toxicity of meloxicam when used in cats for more than 3–6 months at a daily dose of 0.05 mg/kg (Leo et al., 2014; Petrucci et al., 2021), 0.2-0.1-0.025 mg/kg (Borrego et al., 2009) and 0.2-0.1 mg/kg (Charlton et al., 2013; Munday et al., 2022) has been demonstrated.

In the postoperative period, patients of the control group received adjuvant chemotherapy in the DC regimen: "Ebeve" Docetaxel (active substance – docetaxel) + Endoxan (active substance – cyclophosphamide), while the experimental group received the same DC regimen with the addition of Meloxivet (active substance - meloxicam).

The treatment scheme provided for both groups: intravenous "Ebeve" Docetaxel (20 mg/m^2) and Endoxan (200 mg/m^2) on the 7-8th day after mastectomy, followed by 4-6 courses at intervals of 3 weeks. The cats of the experimental group were additionally prescribed Meloxivet at a dose of 0.2 mg/kg orally once a day for 4-6 months.

Table 2 provides basic information on the pharmacological agents that are components of the adjuvant treatment protocol.

Table 1. Composition of the control and experimental groups.

Clinical stage	Group	
	control	experimental
I (T_1 N_0 M_0)	7	8
II (T_2 N_0 M_0)	9	8
III (T_{1-2} N_1 M_0)	9	7
III (T_3 N_{0-1} M_0)	10	9
Total	35	32

Table 2. Characteristics of the constituent components of the protocol.

Preparation	Active substance	Pharmacological group / code ATC*	Producer
Docetaxel "Ebeve"	docetaxel	Antineoplastic agents Alkaloids of plant origin and other preparations of natural origin. Taxanes / Code ATC L01C D02	EBEWE Pharma Ges.m.b.H. Nfg. KG / Unterach am Attersee, Austria
Endoxan	cyclophosphamide monohydrate	Antineoplastic agents. Alkylating compounds Analogues of nitrogen mustard Cyclophosphamide / Code ATCC L01A A01	Baxter Oncology GmbH, Halle/Westfalen, Germany
Meloxyvet	meloxicam	Non-steroidal anti-inflammatory drugs / Code ATCC M01A C06	Ukrzoovetprompostach Kyiv, Ukraine

* – anatomical-therapeutic-chemical classification (ATC)

Table 3. Average survival rates and recurrence-free period.

Clinical stage	Average duration of the period, months	
	Survival	disease-free
Control – mastectomy+docetaxel+cyclophosphamide (*n*=35)		
I (T_1 N_0 M_0), *n*=7	25.6±2.2	14.0±1.8
II (T_2 N_0 M_0), *n*=9	16.8±1.7	12.8±1.9
III (T_{1-2} N_1 M_0), *n*=9	12.9±0.9	7.2±1.0
III (T_3 N_{0-1} M_0), *n*=10	8.3±1.4	4.4±0.5
Experimental – mastectomy+docetaxel+cyclophosphamide+meloxicam (*n*=32)		
I (T_1 N_0 M_0), *n*=8	32.7±2.5***	21.1±2.2***
II (T_2 N_0 M_0), *n*=8	22.4±1.3***	18.1±1.3***
III (T_{1-2} N_1 M_0), *n*=7	17.2±1.0***	13.5±1.6***
III (T_3 N_{0-1} M_0), *n*=9	13.1±1.5***	8.3±0.8***

*** – $P<0.001$, compared to the control (mastectomy+docetaxel+cyclophosphamide)

After the end of the treatment course, further assessment included physical examination of the patients, chest X-ray in three projections (PLX 100, Perlong Medical Equipment), abdominal ultrasound (Toshiba XG (SSA-790A) Aplio XG) every three months during the first year, and once every six months in the following year.

The recurrence-free period was defined as the time interval from the end of treatment to documented progression of

Table 4. Assessment of disease progression depending on the clinical stage.

Clinical stage	Period before progression with metastasis, months					
	<6		6-12		>12	
	n	%	*n*	%	*n*	%
Control - mastectomy+docetaxel+cyclophosphamide (*n*=35)						
I (T_1 N_0 M_0), *n*=7	–	–	3	42.9	4	57.1
II (T_2 N_0 M_0), *n*=9	2	22.2	4	44.5	3	33.3
III (T_{1-2} N_1 M_0), *n*=9	6	66.7	1	11.1	2	22.2
III (T_3 N_{0-1} M_0), *n*=10	7	70.0	2	20.0	1	10.0
Total (*n*=35)	15	42.8	10	28.6	10	28.6
Experimental – mastectomy+docetaxel+cyclophosphamide+meloxicam (*n*=32)						
I (T_1 N_0 M_0), *n*=8	–	–	3	37.5	5	62.5
II (T_2 N_0 M_0), *n*=8	1	12.5	3	37.5	4	50.0
III (T_{1-2} N_1 M_0), *n*=7	2	28.6	4	57.1	1	14.3
III (T_3 N_{0-1} M_0), *n*=9	3	33.3	4	44.5	2	22.2
Total (*n*=32)	6	18.8	14	43.8	12	37.4

the disease, which was manifested by the appearance of recurrences in the surgical intervention area (in the suture area and up to 2 cm around it) or by foci of metastases in regional or distant tissues (Gemignani et al., 2018). Overall survival was defined as the period from the end of the treatment course to the death of the cat, regardless of the cause (Borrego et al., 2009).

Evaluation of the results of the clinical study of cats and the toxicity of chemotherapeutic drugs was carried out according to the following indicators: vomiting, diarrhoea, decreased appetite, anorexia. The main clinical and biochemical blood markers were determined one or two days before the next course of chemotherapy.

The research was carried out in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986), Directive 2010/63/EU of the European Parliament and the Council on the Protection of Animals Used for Scientific Purposes, and the Law of Ukraine "On the Protection of Animals from Cruelty" (2006), which was confirmed by the conclusion of the Bioethics Commission of the Dnipro State Agrarian and Economic University (Protocol no. 2 dated 12 November 2020).

Statistical analysis was performed using the Statistica 10 program (StatSoft Inc., USA, 2011) with their adjustment using the Bonferroni correction. The Kaplan–Meier product restriction method was used to determine disease progression and survival, and differences were assessed by the log-rank test. Values of $P<0.05$ were considered statistically significant.

Results

Clinical approval of meloxivet adjuvant administration to cats with mammary carcinoma showed a significant ($P<0.001$) increase in survival and recurrence-free period (Table 3). In the clinical stages T_1 N_0 M_0; T_2 N_0 M_0; T_{1-2} N_1 M_0, the period from the end of treatment to animal death was

extended by 1.3 times, while in the stage T_3 N_{0-1} M_0 by 1.6 times. The prolongation of the disease-free period with the use of the NSAID was 1.5 times for the T_1 N_0 M_0 stage, 1.4 times for the stage T_2 N_0 M_0, and 1.9 times for T_{1-2} N_1 M_0 and T_3 N_{0-1} M_0.

The prognosis of the disease course, related to its clinical stage, is shown in Table 4. Within 6 months, for stage II T_2 N_0 M_0, meloxivet reduced the level of metastasis by 1.8 times (from 22.2 to 12.5%), stage III T_{1-2} N_1 M_0 by 2.3 times (from 66.7 to 28.6%), and stage III T_3 N_{0-1} M_0 by 2.1 times (from 70 to 33.3%). After 6 to 12 months of using meloxivet, metastatic stage progression was reduced in cats with stage T_{1-2} N_1 M_0 by 5.1 times, and with T_3 N_{0-1} M_0 by 2.2 times. After 12 months and more, the probability of progression in case of using a NSAID decreased for the T_2 N_0 M_0 stage by 1.5 times (from 50 to 33.3%), for T_3 N_{0-1} M_0 by 2.2 times (from 22.2 to 10%) against the background of an increase for T_{1-2} N_1 M_0 by 1.6 times (from 14.3 to 22.2%).

The dynamics of disease progression in cats of different ages was determined depending on the treatment regimen (Table 5). In cancer-stricken cats up to 3 years of age, the inclusion of meloxivet ensured the absence of metastasis during the first 6 months and delayed the progression of the disease for at least 12 months. The use of the proposed treatment scheme in 3- to 5-year-old patients reduced the frequency of cancer cell dissemination within six months by 1.3 times (from 37.5 to 28.6%), in 5- to 9-year-old animals by 2.3 times (from 46.2 to 20%), and for those older than 9 years by 2.8 times (from 55.6 to 20%). In the period from 6 to 12 months, the number of cats in which the development of metastases was diagnosed against the background of meloxivet administration was greater compared to the control group: in 5- to 9-year-old individuals by 1.7 times, and in those older than 9 years by 1.8 times. In general, during the first 6 months after treatment, meloxivet caused

Table 5. Effectiveness of treatment in cats of different age groups.

Age, years	Period before progression with metastasis, months					
	<6		6-12		>12	
	n	%	*n*	%	*n*	%
Control – mastectomy+docetaxel+cyclophosphamide (*n*=35)						
<3 (*n*=5)	1	20.0	1	20.0	3	60.0
3-5 (*n*=8)	3	37.5	3	37.5	2	25.0
5-9 (*n*=13)	6	46.2	3	23.1	4	30.7
>9 (*n*=9)	5	55.6	3	33.3	1	11.1
Total (*n*=35)	15	42.8	10	28.6	10	28.6
Experimental – mastectomy+docetaxel+cyclophosphamide+meloxicam (*n*=32)						
<3 (*n*=5)	-	-	1	20.0	4	80.0
3-5 (*n*=7)	2	28.6	3	42.8	2	28.6
5-9 (*n*=10)	2	20.0	4	40.0	4	40.0
>9 (*n*=10)	2	20.0	6	60.0	2	20.0
Total (*n*=32)	6	18.8	14	43.8	12	37.4

a 2.3-fold reduction in the risk of progression (from 42.8 to 18.8%). In patients receiving this therapy, in most cases metastases were registered in the period from 6 to 12 months or after 12 months. The number of such animals was 1.5 and 1.3 times higher than with the corresponding indicators in the control group, respectively.

Analysis of the clinical effectiveness of the treatment regimens also included an assessment of the risk of complications, which in the case of a severe course can justify contraindications to the further use of chemotherapeutic agents (Table 6).

The use of meloxivet reduced the probability of vomiting by 1.6 times, decreased appetite by 1.5 times, and anorexia by 1.4 times.

Monitoring of patients carried out for two years after the end of treatment made it possible to determine the features of the development of metastatic foci (Table 7). As the data show, the use of NSAIDs reduced the risk of recurrence by 1.5 times, without significantly affecting the localisation of distant metastases.

Discussion

The increased use of nonsteroidal anti-inflammatory drugs in small animals has led to the development of new and innovative drugs in this drug class: etodolac, carprofen, ketoprofen, meloxicam, deracoxib, and tepoxalin (Curry et al., 2005). The results obtained received are important given the need for a deeper study of their mechanisms of action, pharmacokinetics, pharmacological effects and possible side effects.

Table 6. Adverse effects of the treatment of cats with malignant mammary tumours.

Indicator	Mastectomy					
	Control docetaxel+cyclophosphamide (*n*=35)			Experimental docetaxel+cyclophosphamide+ meloxicam (*n*=32)		
	n	%	95% CI (%)	*n*	%	95% CI (%)
Vomiting	7	20.0	17-23	4	12.5	9-16
Diarrhea	5	14.3	11-19	5	15.6	11-20
Decreased appetite	8	22.9	19-27	5	15.6	12-18
Anorexia	6	17.1	13-21	4	12.5	9-15

Table 7. Peculiarities of disease progression for breast carcinoma.

Indicator		Group			
		control (*n*=35)		experimental (*n*=32)	
		n	%	*n*	%
Local recurrence		5	14.3	3	9.4
Metastasis	lungs	17	48.6	14	43.7
	bones	7	20.0	6	18.8
	lymph odes	6	17.1	8	25.0
	other tissues	5	14.3	4	12.5

Despite the fact that cyclooxygenase-2 is overexpressed in the majority of feline mammary carcinomas (87%), information about it, unlike in humans and dogs, is limited and controversial (Sayasith et al., 2009). Specifically, Beam et al. (2003) justified the insufficient effectiveness of NSAIDs by the low frequency of expression of cyclooxygenase-2. Our results are consistent with the importance of NSAIDs in cats with mammary tumours. The more detailed study of the expression of cyclooxygenase-2 in the last ten years has changed the position of clinicians regarding the importance of its role in malignant tumours in cats.

The tumourigenic activity of PG E2 (PGE2) has now been confirmed (Szweda et al., 2020) to be controlled by cyclooxygenase-2 (COX-2) and microsomal PGE synthase-1 (mPGES-1). The frequency of expression of COX-2, EP2 receptors and mPGES-1 was significantly higher in carcinomas compared to non-neoplastic tissues and adenomas (Millanta et al., 2016), justifying the use of meloxivet in cats with mammary malignancies.

Our positive clinical results were contrary to the data published by Borrego et al. (2009), in which the long-term use of meloxicam in cats with mammary adenocarcinoma in the setting of surgery and chemotherapy did not significantly prolong Kaplan-Meier median survival time and median disease-free interval, which were 460 and 269 days, respectively.

The possibility of long-term use of NSAIDs in cats has been confirmed by many studies. According to data on the good tolerance of meloxicam at a daily dose of 0.029 mg/kg when used for 1814 days, adverse effects were recorded in only 18% of patients after an average time of 448 days (Charlton et al., 2013). The effectiveness of postoperative administration of meloxicam and its minimal effect on clinical and biochemical blood parameters was also confirmed by Kamata et al. (2012).

Gowan et al. (2011) demonstrated the possibility of long-term meloxicam administration at a maintenance dose of 0.02 mg/kg even in cats with chronic renal failure (provided a stable general clinical condition). Meanwhile, long-term therapy with meloxicam can slow the progression of kidney disease (in particular, chronic renal failure) in some cats. Long-term treatment with oral meloxicam did not reduce life expectancy in cats with pre-existing stable chronic renal failure, even in cats with stage II and III IRIS, suggesting that it should be considered part of a therapeutic regimen to improve the quality of life and longevity in cats with chronic disease states (Gowan et al., 2012). Appointment of meloxivet for 6 months was not accompanied by pronounced side effects, confirming the possibility of long-term use of NSAIDs.

The clinical effectiveness of low doses of meloxicam (daily oral dose of 0.02 mg/kg) in cats with tumours (characterised by a decrease in neoplasia size and the level of pain response, improvement in quality of life) and the absence of critical kidney function disorders were outlined by Keepman and Pellin (2022), which is consistent with our results.

Cyclooxygenase-2 expression, observed in 96% of invasive feline mammary carcinomas, is associated with a worse prognosis (P=0.002), as confirmed by its correlation with ER-negative status (P=0.04), increased PR expression (P=0.038), and increased angiogenesis, assessed by VEGF expression (P=0.002) (Millanta et al., 2006). Positive clinical results of meloxivet application in cats with mammary gland malignancies are consistent with the correlation of cyclooxygenase-2 expression level and disease prognosis.

Despite the overall unfavourable prognosis, adjuvant treatment may be an

option to reduce the risk of metastasis, as also indicated by other researchers (Petrucci et al., 2021).

The obtained positive effect of using meloxivet is likely due to the analgesic effect on the surgical wound and optimisation of the healing process. The high efficiency of postoperative meloxicam at a dose of 0.03 mg/kg with a small number of side effects was shown by Robertson and Taylor (2004).

Thus, the obtained data complement and expand the available information regarding the use of NSAIDs for malignant mammary neoplasms in cats. Combined chemotherapy using docetaxel and cyclophosphamide in combination with meloxivet is indicated against the background of surgical intervention in cats for malignant mammary tumours.

Conclusions

The inclusion of meloxivet nonsteroidal anti-inflammatory agent in the adjuvant chemotherapy protocol in the DC regimen (docetaxel+cyclophosphamide) in cats with clinical stage I-III mammary gland carcinomas prolonged ($P<0.001$) the duration of survival and the relapse-free period. The use of meloxivet in the complex treatment of cats with mammary gland carcinoma reduced the risk of metastasis, depending on the clinical stage of the disease, in the first 6 months by 1.8–2.3 times, after 6–12 months by 2.2–5.1 times, and more than 12 months by 1.5–2.2 times. The use of meloxivet NSAID against the background of bilateral mastectomy and chemotherapy with the DC regimen provided a 1.5-fold reduction in the risk of relapse in the surgical intervention area. Increasing age of cats with mammary gland carcinoma worsens the prognosis of the disease against the background of a reliable increase in the effectiveness of treatment when meloxivet NSAID is included in the protocol.

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Klinička procjena učinkovitosti meloxiveta u kompleksnom liječenju mačaka s karcinomom mliječne žlijezde

Dmytro BILYI, DVM, Professor, Maksym HERHAULOV, Postgraduate, Faculty of Veterinary Medicine, Dnipro State Agrarian and Economic University, Dnipro, Ukraine

Ovaj rad predstavlja rezultate kliničkog istraživanja metronomske uporabe meloxivet nesteroidnog protuupalnog lijeka u usporedbi s DC (docetaksel + ciklofosfamid) režimom polikemoterapije nakon bilateralne mastektomije u mačaka s karcinomom mliječne žlijezde. Uključivanje meloxivet nesteroidnog protuupalnog lijeka u metronomski režim u kompleksnoj kemoterapiji kod bilateralne mastektomije zbog karcinoma mliječne žlijezde pouzdano omogućuje (P<0,001) poboljšanje rezultata liječenja. Posebice, produljenje razdoblja preživljavanja u kliničkoj fazi T_1 N_0 M_0 (s 25,6±2,2 na 32,7±2,5 mjeseci), T_2 N_0 M_0 (s 16,8±1,7 na 22,4±1,3 mjeseca), T_{1-2} N_1 M_0 (s 12,9±0,9 na 17,2±1,0 mjesec) za 1,3 puta, III (T_3 N_{0-1} M_0) za 1,6 puta (s 8.3±1.4 na 13,1±1,5 mjeseci) i razdoblje bez bolesti za 1,5 (s 14,0±1,8 na 21,1±2,2 mjeseca), 1,4 (s 12,8±1,9 na 18,1±1,3 mjeseca), 1,9 (s 7,2±1,0 na 13,5±1,6 mjeseci), odnosno 1,9 puta (s 4,4±0,5 na 8,3±0,8 mjeseci). Kompleksno liječenje mačaka koje je uključivalo nesteroidnu protuupalnu terapiju, ovisno o kliničkoj fazi tijekom prvih šest mjeseci nakon završetka tretmana s 22,2-70,0 % na 12,5-33,3 % smanjilo je rizik od progresije bolesti. Istovremeno, zamijećen je povećani broj pacijenata u kojih su se metastaze pojavile kasnije (nakon šest do dvanaest mjeseci). Uporaba meloxivet nesteroidnog protuupalnog lijeka omogućila je izbjegavanje progresije bolesti u mačaka do tri godine starosti te smanjenje vjerojatnosti i odgodu nastanka metastaza u svim dobnim kategorijama. Predložena shema liječenja mačaka s karcinomima mliječne žlijezde omogućila je smanjenje razine nuspojava, pokazujući beznačajan rizik od negativnih nuspojava na tijelo zbog dugoročne uporabe meloxiveta u odnosu na smanjenje učestalosti ponavljanja u kirurškom interventnom području za 1,5 puta.

Ključne riječi: *mačke tumori, mliječna žlijezda, nesteroidni protuupalni lijekovi, kemoterapija, mastektomija*