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### Efficacy of COP-based protocol used with raltegravir in treatment of cats with mediastinal lymphoma and progressive viral leukemia

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**Abstract.** Mediastinal lymphoma is a common disease in both human and veterinary medicine and is frequently diagnosed in cats infected with feline leukemia virus. The disease is considered a negative prognostic factor for affected animals. The retrospective research included 5 FeLV-positive cats with confirmed mediastinal lymphoma and progressive viral leukemia. The purpose was to study the response of FeLV-positive cats to standard chemotherapy protocol: cyclophosphamide 250 mg/m<sup>2</sup> IV, vincristine 0.5 mg/m<sup>2</sup> IV, prednisolone 20...40 mg/m<sup>2</sup> orally (COP), survival of animals and side effects associated with chemotherapeutic treatment. All studied cats received raltegravir (Isentress, MSD, USA) orally at a dose of 20 mg/kg every 12 hours. Improvement in clinical signs associated with mediastinal lymphoma was observed after the 3rd course of chemotherapy. The clinical response rate was 80 % (40 % full remission, 40 % partial remission, 20 % unchanged status). The average lifespan of FeLV-positive cats treated with chemotherapy for mediastinal lymphoma was 1091.2 days, with a maximum lifespan of 1364 days and a minimum lifespan of 775 days. Rate of clinical response, as well as lifespan expectancy of affected cats, was higher than in previous studies. This is probably due to raltegravir, which can reduce the viral load and thus control the course of progressive infection. Side effects were found in 100 % of FeLV-positive cats: with anorexia — in two animals (60 %), vomiting — in two (40 %), neutropenia — in four (80 %), thrombocytopenia — in all cats (100 %), anemia — in three (60 %) and azotemia — in one

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animal (20 %). Overall, the efficacy of the COP protocol was satisfactory, and chemotherapy treatment can be offered to owners of FeLV-positive cats with mediastinal lymphoma, if the owner is reluctant to opt for euthanasia of the affected animal.

**Keywords:** oncology, leukemia, antiretroviral therapy, chemotherapy, anemia, small pets

**Conflicts of interest.** The authors declared no conflicts of interest. The owners of the studied animals purchased medications on their own in private pharmacies in Moscow.

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## Introduction

Mediastinal lymphoma is one of the most common oncological diseases leading to death of small domestic animals [1]. At the same time, complications caused by feline leukemia virus (FeLV) increase the likelihood of lymphoma by approximately 60 times, and mediastinal lymphoma is the most frequently diagnosed type of FeLV-associated lymphoma [2]. It should be noted that the clinical symptoms of lymphoma reflect respiratory distress associated with presence of pleural effusion in chest cavity and, as a result, can lead to death of the animal [3].

Several chemotherapy treatment protocols have been developed for the treatment of cats with lymphoma [4]. Meanwhile, both the level of clinical response and survival of cats with lymphoma had no significant differences when using the COP protocol (cyclophosphamide, vincristine and prednisolone) and the Madison Wisconsin Protocol (asparaginase, prednisolone, cyclophosphamide, doxorubicin) [5]. Side effects associated with chemotherapy treatment develop 24...48 hours after the start of therapy, as well as 2–14 days in case of delayed drug effects [6].

The progressive form of FeLV is the cause of such concomitant pathologies as impaired hematopoiesis, oncological diseases, and immunosuppressive conditions [7]. Due to the risk of developing these pathologies, raltegravir (Isentress, MSD, USA) is increasingly being prescribed to infected cats. Raltegravir is an inhibitor of human immunodeficiency virus (HIV) integrase enzyme, affects integration of the virus into the host cell genome, and has a similar effect on integrase of feline leukemia virus (FeLV) [8]. Moreover, there are studies proving the effectiveness of raltegravir in reducing the level of viral load, which in turn affects the course of FeLV infection and clinical signs associated with the disease [9].

Thus, **the research was conducted to study** the level of clinical response of FeLV-positive cats with progressive infection and mediastinal lymphoma, treated with raltegravir under the COP protocol, as well as to study the side effects and lifespan of the studied animals.

## Materials and methods

The study included 5 FeLV-positive cats with progressive infection observed in private veterinary clinic in Moscow from June 2022 to June 2023. The following study criteria were documented: gender; age; breed; reproductive status; level of clinical response to chemotherapy treatment; side effects associated with chemotherapy; lifespan (in days) considering the chemotherapy.

The progressive form of FeLV infection was confirmed by positive results of polymerase chain reaction (PCR) and enzyme immunoassay (ELISA) tests, carried out twice with an interval of 3 months. Due to progressive infection, all cats received 20 mg/kg raltegravir orally every 12 hours. The control of FeLV, namely anemia and immunosuppression, was satisfactory in all animals.

Mediastinal lymphoma in the studied cats was confirmed with a specific clinical picture characterized by hydrothorax and respiratory distress, as well as by specific diagnostics — chest X-ray, effusion cytology, and contrast-enhanced computed tomography (CT) of chest with biopsy of the pathological material with its further histological examination [10]. All cats with confirmed mediastinal lymphoma received chemotherapy according to the COP protocol: cyclophosphamide (Endoxan, Baxter, USA) at 250 mg/m<sup>2</sup> IV, vincristine (Vincristine-Teva, Teva, Israel) at 0.5 mg/m<sup>2</sup> IV, prednisone (Elfa Prednisolone, Elfa, Russia) at 20...40 mg/m<sup>2</sup> orally [11]. Four studied animals (80 %) received 5 courses of the COP protocol and one cat (20 %) received 3 courses.

## Results and discussion

Lymphoma is still a major problem for veterinary medicine around the world. So, its diagnosis is often difficult, and possibilities of therapy are limited. Nevertheless, the COP chemotherapeutic protocol is one of the most promising protocols for the treatment of lymphoma, especially for cats with FeLV [5].

A retrospective analysis of the COP chemotherapeutic protocol administered to FeLV-positive cats with progressive infection treated with raltegravir to control viral load showed the following results.

The study included 5 FeLV-positive cats (Table 1), all animals (100 %) were neutered, three cats (60 %) were male and two (40 %) were female. The median age at diagnosis of mediastinal lymphoma was 719.2 days (minimum age 775 days, maximum age 1364 days). In all cats (100 %), lymphoma was diagnosed only in the mediastinum, other localizations, as well as distant foci of metastasis, were not detected.

Table 1

Characteristics of FeLV-positive cats studied

Cat No.	Gender	Intact status	Breed
1	♂	Castrated	Burmese
2	♂	Castrated	Metis
3	♂	Castrated	Metis
4	♀	Castrated	Maine Coon
5	♀	Castrated	Metis

All the studied cats, after the final diagnosis of mediastinal lymphoma, were referred for chemotherapeutic treatment. In view of the described efficacy and availability of medications, the veterinarians chose the COP protocol [5]. Data characterizing chemotherapy treatment for mediastinal lymphoma and FeLV infection are given in Table 2.

Table 2

**Characteristics of chemotherapy treatment in FLV-positive cats with mediastinal lymphoma**

Cat No.	Age of diagnosis, days	Survival time, days	Lymphoma type	Number of chemotherapy courses	Clinical response
1	403	775	Mediastinal	5	Partial remission
2	930	1209	Mediastinal	5	Partial remission
3	248	1116	Mediastinal	5	Full remission
4	713	992	Mediastinal	5	Full remission
5	1302	1364	Mediastinal	3	Absence

The rate of clinical response to chemotherapy was 80 %, while only 20 % of the studied cats did not respond to chemotherapy treatment, and by the end of the study, death of one cat was recorded. In the rest of the cats, both full remission and partial remission were observed. At the same time, the average life span of FeLV-positive cats (372 days) was higher than in previous studies [3]. Probably, the intake of raltegravir, an inhibitor of HIV and FeLV integrase, was one of the factors that had a positive effect on this parameter. Thus, taking raltegravir decreased viral load in FeLV-infected cats, which affected the incidence of complications associated with progressive infection [12]. In addition, this medication is well tolerated by cats and is not associated with any life-threatening side effects other than transient anorexia [12].

Studies have shown that despite the high level of clinical response, several side effects were described in all studied animals: anorexia, neutro- and thrombocytopenia, anemia, azotemia and vomiting. Characteristics of side effects associated with chemotherapy treatment were given in Table 3.

Table 3

**Side effects associated with chemotherapy treatment**

Cat No.	Side effects					
	Anorexia	Anemia	Thrombocytopenia	Neutropenia	Azotemia	Vomiting
1		+	+	+		
2	+		+	+		
3	+	+	+	+		+
4		+	+	+		
5	+		+		+	+

Thrombocytopenia was found in 100 % of FeLV-positive cats treated with chemotherapy according to the COP protocol. It is worth noting that thrombocytopenia in all cats did not affect quality of life of the animals and was not associated with the occurrence of spontaneous bleeding in any animal. It is likely that the true incidence of thrombocytopenia during chemotherapy treatment could be much lower, since manual platelet counts were not performed for all studied cats, and platelet aggregation with the anticoagulant K3EDTA could falsely increase the incidence of thrombocytopenia in FeLV-positive cats undergoing chemotherapy treatment. Along with this, neutropenia has become one of the most common side effects (80 %) associated with chemotherapy. However, this phenomenon in many cats proceeded in a mild form and required correction by introduction of human granulocyte colony-stimulating factor (Neypomax, PHS Pharm-standard, Russia) if the level of leukocytes fell below the level of  $2 \cdot 10^9/l$  [13]. The anorexia noted in animals (60 %) was a predictable side effect of the COP chemotherapy protocol, which was corrected by oral administration of appetite stimulating drugs, for example, tetracyclic antidepressant mirtazapine (Mirtazapine Kanon, Canonpharma, Russia) [14]. In addition, it can be assumed that anemia and azotemia reported in several cats (60 %) also negatively affected the incidence of anorexia in FeLV-positive cats. At the same time, anemia was of a non-regenerative nature and was subjected to medical correction (taking drugs from the group of poe-tins and blood transfusion) in case of its life-threatening values (hematocrit less than 15 %) [15]. According to the IRIS III classification, azotemia was found in one cat (20 %), which prevented the veterinarian from conducting a full cycle of chemotherapy courses and, together with the lack of a clinical response to the treatment, caused the death of the animal.

It should be noted that only 40 % of cats were diagnosed with vomiting, while in one cat it could be associated with azotemia and be a consequence of intoxication due to uremia.

## Conclusions

Thus, the COP chemotherapeutic protocol was generally well tolerated by FeLV-positive cats with mediastinal lymphoma, and the level of clinical response to it was comparable to that of uninfected cats demonstrated in previously published research. Side effects associated with chemotherapy treatment were predictable and manageable, allowing treatment to be completed in 80 % of the animals in the study. In addition, the lifespan of FeLV-positive cats with mediastinal lymphoma was longer than in previous studies. This phenomenon may be associated with raltegravir, which reduced viral load in FeLV infected cats and, thus, improved prognosis for diseased animals. Based on this, raltegravir should be administered to all FeLV-positive cats with a progressive form, both before and after the onset of comorbid conditions. At the same time, more research is needed on the treatment of advanced feline leukemia virus infection and associated diseases in order to improve quality of life of infected cats.

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## Эффективность СОР-протокола при средостенной лимфоме у кошек с прогрессивной вирусной лейкемией, принимавших ралтегравир

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**Аннотация.** Лимфома средостения — часто встречающееся заболевание как в гуманной, так и ветеринарной медицине, при этом данное заболевание часто диагностируют в популяции кошек, больных вирусной лейкемией (ЛК). Наличие вируса лейкемии кошек (ВЛК) считается негативным прогностическим фактором для больных животных. Цель ретроспективного исследования, включавшего 5 ВЛК-положительных кошек с подтвержденной средостенной лимфомой и прогрессивной формой вирусной ЛК, — изучение ответа ВЛК-положительных кошек на стандартный химиотерапевтический протокол: циклофосфамид 250 мг/м<sup>2</sup> в/в, винкристин 0,5 мг/м<sup>2</sup> в/в, преднизолон 20...40 мг/м<sup>2</sup> п/о (СОР), продолжительности жизни животных и побочных эффектов, связанных с химиотерапевтическим лечением. Все исследуемые кошки получали ралтегравир (“Исентресс”, MSD, США) п/о в дозе 20 мг/кг каждые 12 ч. Улучшение клинических признаков, ассоциированных со средостенной лимфомой, наблюдали после 3-го курса химиотерапии. Уровень клинического ответа составил 80 % (40 % — полная ремиссия, 40 % — частичный ответ, 20 % — отсутствие положительной динамики). Средняя продолжительность жизни ВЛК-положительных кошек, получавших химиотерапевтическое лечение против средостенной лимфомы, составила 1091,2 день, максимальная продолжительность жизни — 1364 дня, минимальная — 775 дней. Уровень клинического ответа, а также продолжительность жизни больных кошек оказались выше, чем в предыдущих исследованиях. Вероятно, это связано с приемом ралтегравира, способного снизить вирусную нагрузку при вирусной ЛК и таким образом контролировать течение прогрессивной инфекции. Побочные эффекты были обнаружены у 100 % ВЛК-положительных кошек, при этом анорексия была обнаружена у двух (60 %), рвота — у двух (40 %), нейтропения — у четырех (80 %), тромбоцитопения — у всех кошек (100 %), анемия — у трех (60 %) и азотемия — у одной (20 %). В целом эффективность СОР-протокола была удовлетворительной, что позволяет ветеринарным специалистам предлагать химиотерапевтическое лечение владельцам ВЛК-положительных кошек, больных средостенной лимфомой, если владелец не склонен выбирать эвтаназию больного животного.

**Ключевые слова:** онкология, лейкоз, антиретровирусная терапия, химиотерапия, анемия, мелкие домашние животные

**Заявление о конфликте интересов.** Автор заявляет об отсутствии конфликта интересов. Владелец исследуемых животных приобретали лекарственные препараты самостоятельно в частных аптеках г. Москвы.

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