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Retrospective Study of Adverse Events of Chemotherapy in Cats

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ABSTRACT

***Background*:** Clients who seek veterinary care for pets with cancer are often concerned about the potential negative impact of chemotherapeutic treatments on their animals' quality of life. A consensus currently exists in veterinary oncology regarding the quantification and rating of adverse treatment effects in dogs and cats in response to chemotherapy agents. This grading system is referred to as Veterinary Cooperative Oncology Group - Common Terminology Criteria for Adverse Events. The purpose of this retrospective case series was to investigate the delayed acute effects of chemotherapy drugs in cats receiving cancer treatment.

***Materials, Methods & Results*:** Medical records were reviewed to determine the chemotherapy agent used and delayed adverse effects. Side effects were classified according to Veterinary Co-operative Oncology Group grading. All cats were evaluated after the first chemotherapy administration, after a single dose. The reported effects included hematologic effects (e.g., neutropenia, thrombocytopenia, increases in liver enzymes, and azotemia), gastrointestinal effects (e.g., vomiting, diarrhea, and inappetence), and sepsis. All of the cats in this study received ondansetron and omeprazol in the first five days following chemotherapy administration. If vomiting occurred with oral medication, maropitant was administered subcutaneously for three consecutive days. If diarrhea (> grade II) occurred, probiotics were administered for seven days. Hematologic examination was performed 3-14 days after chemotherapy. If neutropenia (> grade III) occurred, Human granulocyte colony stimulating factor was administered subcutaneously for three consecutive days together with prophylactic antibiotics. Lomustine, carboplatin, vincristine, doxorubicin, cyclophosphamide, mitoxantrone, and vinblastine were administered in 33%, 19%, 16%, 5%, 16%, 10% and 2% of the cases examined, respectively. The most common adverse events were vomiting, inappetence, neutropenia, and thrombocytopenia. Vomiting occurred in 6% cases, most of them associated with cyclophosphamide. Inappetence/anorexia affected 12% of the cases, mostly those involving cyclophosphamide or doxorubicin. Neutropenia was observed in 22% of the cases, with cyclophosphamide, followed by carboplatin and lomustine. According to the current grading system of adverse effects induced by chemotherapy, grade I toxicity was observed in 83% of the cases, whiles grade II-IV were observed in 7%, 8%, and 2% of the cases examined, respectively.

***Discussion*:** In general, the chemotherapy regimens in the cases examined were well tolerated. The toxicity experienced was infrequent and mostly mild, thereby resulting in satisfactory tolerability of the chemotherapy regimens. According to the current grading system for the adverse effects of chemotherapy, 83% of the cases examined included grade I, indicating that most of the cats experienced asymptomatic, or mild symptoms, and medical intervention was not needed. In previous studies of dogs and cats, a severe adverse event following chemotherapy was reported for fewer than 1 in 4 animals, and approximately 3-5% experienced a serious adverse event that led to hospitalization. In the present study, 2% of the cats experienced serious or life threatening adverse events. The only chemotherapeutic agent that was associated with inappetence, vomiting, and neutropenia was cyclophosphamide. Based on the data examined, we would recommend that cyclophosphamide should be used with caution for the treatment of cancer in cats, with adequate antiemetic and nutritional support available if needed. In addition, febrile neutropenia/sepsis may be avoided by using a fractionated schedule.

Keywords: feline, oncology, chemotherapy, side effects, tolerability.

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INTRODUCTION

Clients who seek veterinary care for pets with cancer are often concerned about the potential negative impact of chemotherapeutic treatments on their animals' quality of life [14,16]. The toxicity profiles associated with anticancer agents have included immediately evident toxicities (e.g., those that develop within 24-48 h after treatment), acute delayed effects (e.g., those that develop within 2-14 days after treatment), and/or cumulative/chronic toxicity (effects extending over weeks, months, or years). Delayed acute effects from chemotherapy often include bone marrow suppression and nausea, vomiting, and diarrhea. In the majority of instances, these effects are self-limiting and the incidence of hospitalization for such problems is low [4]. Examples of potential cumulative and/or chronic toxicity include hepatic dysfunction after multiple doses of cyclohexylchloroethylnitrosourea (CCNU, also known as lomustine), cardiac abnormalities after exceeding a usually safe cumulative dose of doxorubicin, and renal disease after administration of doxorubicin in cats [4].

A consensus currently exists in veterinary oncology regarding the quantification and rating of adverse treatment effects in dogs and cats in response to chemotherapy agents. This grading system is referred to as Veterinary Cooperative Oncology Group - Common Terminology Criteria for Adverse Events (VCOG--CTCAE) [15]. The purpose of this retrospective case series was to investigate the delayed acute effects of chemotherapy drugs in cats receiving cancer treatment.

MATERIALS AND METHODS

Medical records

This retrospective study involved 112 cats treated with chemotherapy between August 2011 and August 2016 at Oncopet Veterinary Clinic (Rio de Janeiro, Brazil). All of the cats were previously diagnosed with malignant neoplasia and chemotherapy was prescribed as a definitive and/or adjuvant treatment.

Medical records were reviewed to determine the chemotherapy agents used and the delayed acute toxicity effects observed between 12 h and 21 d after the administration of chemotherapy. The chemotherapy agents administered included vincristine, vinblastine, lomustine, cyclophosphamide, doxorubicin, mitoxantrone, and carboplatin, according to neoplasm histologic type, treatment protocol, comorbidities. All cats were evaluated after the first chemotherapy administration, after a single dose. For example, vincristine was evaluated in cats receiving OP protocol, after first time the cat received this chemotherapy. However, cyclophosphamide was evaluated in cats receiving COP protocol, and it was started as a 4-day cycle after 2 days of vincristine. The reported effects included hematologic effects (e.g., neutropenia, thrombocytopenia, increases in liver enzymes, and azotemia), gastrointestinal effects (e.g., vomiting, diarrhea, and inappetence), and sepsis. A summary of the adverse events grading is provided in Table 1. Late, cumulative, and/or chronic toxicity (e.g., hepatic dysfunction, cardiac abnormalities, and chronic renal disease) were not studied, due to the fact that this retrospective study involved only the follow-up of cats after a chemotherapy single dose, and for a short period of time.

The following factors were statistically examined to determine their relationship to the chemotherapy agents used and their impact on the owners' opinions about treatment: age (< 7 y, 8-11 y, or > 12 y), breed (divided into mixed breed, Siamese, Maine Coon, Ragdoll, and Persian), neoplasm histologic type (lymphoma, carcinoma, mast cell tumor, melanoma, sarcoma, thymoma), and presence of concomitant disease (retroviral, endocrine, cardiovascular, renal, gastrointestinal).

Side effects classification

Side effects were classified according to VCOG-CTCAE grading of adverse effect severity [15] as follows: grade I (asymptomatic, or mild symptoms; clinical signs or diagnostic observations only; intervention not indicated); grade II (moderate; minimal, outpatient, or noninvasive intervention indicated; moderate limitation of daily living activities); grade III (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; significantly limited daily living activities); grade IV (life-threatening consequences; urgent interventions indicated), and grade V (death related to adverse events).

All of the cats in this study received prophylactic and supportive treatment according to the same protocol. Animals receiving chemotherapy received ondansetron (Vonau®)[1] administered at a dose of 0.5 mg kg^{-1} orally, BID, and omeprazol (Gaviz®)[2] at a dose of 1 mg kg^{-1} orally, SID, in the first five days following chemotherapy

Table 1. Common terminology criteria for adverse events following chemotherapy or biological antineoplastic therapy in cats, of Veterinary cooperative oncology group.

Adverse Event	Grade				
	I	II	III	IV	V
Neutropenia (µL−1)	1,500 to <LLN	1,000-1,499	500-999	<500	Death
Thrombocytopenia (µL−1)	100,000 to <LLN	50,000-99,000	25,000-49,000	<25,000	Death
Creatinine	>1.0-1.5× bl	>1.5-3.0× bl	>3.0× bl	>3.0× bl	-
ALT	>ULN to 1.25× ULN	>1.25-1.5× ULN, transient (<2 weeks)	>1.5-2.0× ULN	>2.0× ULN	-
Anorexia	Coaxing or dietary change required to Maintain appetite	Oral intake altered (≤3 days) without significant weight loss; oral nutritional supplements/appetite stimulants may be indicated	Of >3 days duration; associated with significant weight loss (≥10%) or malnutrition; IV fluids, tube feeding or force feeding indicated	Life-threatening consequences; TPN indicated; >5 days duration	Death
Vomiting	<3 episode in 24 h, medical intervention not indicated	3-10 episodes in 24 h; <5 episodes/day for ≤48 h; parenteral fluids (IV or SC) indicated ≤48 h; medications indicated	Multiple episodes >48 h and IV fluids or PPN/TPN indicated >48 h	Life-threatening (e.g.haemodynamic collapse)	Death
Diarrhea	Increase of up to 2 stools per day over bl; no increase in frequency, however, consistency decreased	Increase of 3-6 stools per day over bl; medications indicated; parenteral (IV or SC) fluids indicated ≤48 h; not interfering with ADL	Increase of >6 stools per day over baseline; incontinence >48 h; IV fluids >48 h; hospitalization; interfering with ADL	Life-threatening (e.g.haemodynamic collapse)	Death

LLN = lower limit of normal; ULN = upper limit of normal; bl = baseline; ADL = activities of daily living (eating, sleeping,defecating and urinating).

administration, independent of the chemotherapy drug administered. If vomiting occurred with oral medication, maropitant (cerenia®)[3] at a dose of 2 mg kg $^{-1}$ was administered subcutaneously, SID, for three consecutive days, as oral medication was maintained. In addition, the animals were fed a special diet in case of vomiting/anorexia (Hill´s Prescription a/d®)[4] or (Royal Canin Gastrointestinal®)[5]. When necessary, feeding was forced, and in some cases, an e-tube was recommended. If diarrhea (> grade II) occurred, probiotics were administered for seven days. Hematologic examination was performed 3-14 days after chemotherapy. If neutropenia (> grade III) occurred, Human granulocyte colony stimulating factor (Filgrastim®)[6] at a dose of 5 ug kg^{-1} was administered subcutaneously for three consecutive days together with prophylactic antibiotics.

Statistical analysis

A database exploratory analysis was performed and comparisons between variables were made with the Pearson Chi-square, Kruskal-Wallis, and Mann-Whitney tests as appropriate. Descriptive statistics served as a basis for interpretation of the results. The level of statistical significance was 5%. Tests and studies were performed with the software, Statistical Package for the Social Sciences (SPSS; version 20.0, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 112 oncologic records of various feline breeds were reviewed. The breeds included: mixed (n = 93), Siamese (n = 13), Persian (n = 2), Maine Coon (n = 2), and Ragdoll (n = 2). Forty-three animals (38%) were older than 12 years, while 42 (38%) ranged from 1-7 years in age and 27 (24%) were 8-12 years of age. There was no statistically significant difference between age and adverse events of chemotherapy in the present study.

The neoplasm histological types were highly variable and were categorized as: carcinoma [mammary (13/112), cutaneous squamous cell (3/112), cutaneous basal cell (1/112), bladder transitional cell (1/112), and hepatocellular (1/112)], sarcoma [soft tissue (11/112), chondrosarcoma (2/112), and hemangiosarcoma (1/112)], lymphoma (68/112), visceral mast cell tumor (5/112), melanoma (3/112), thymoma (2/112), and heart base tumor (1/112). Chemotherapy was recommended as a definitive treatment in 39% cats and adjuvant treatment in 61% of the examined cases. Comorbidities were present in 55 (49%) animals, and these included renal disease (14/55) and retroviral diseases (feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) [41/55].

Various chemotherapy agents were administered. The most prevalently used was lomustine, which was applied in 37 (33%) cases. The other agents that were administered included carboplatin in 21 (19%) cases, vincristine in 18 (16%) cases, doxorubicin in five (5%) cases, cyclophosphamide in 18 (16%) cases, mitoxantrone in 11 (10%) cases, and vinblastine in two (2%) cases. The doses were 50 mg/m^2 orally for lomustine, 180 mg/m^2 intravenously for carboplatin, 0.75 mg/m^2 intravenously for vincristine, 2 mg/m^2 intravenously for vinblastine, 1 mg/kg intravenously for doxorubicin, and 5.5 mg/m^2 intravenously for mitoxantrone. Cyclophosphamide was administered orally at a dose of 200 mg/m^2 that was divided into four daily doses (50 mg/m^2 each). These doses are consistent with those previously published, although author's preference determined the dose.

Blood exams, including hematologic examination and biochemistry [blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), and alkaline phosphatase (ALP)], were performed for each animal 7-21 days after chemotherapy administration. For example, the animals that received lomustine (CCNU) underwent their exams on day 7 and day 21. For the animals that received carboplatin, blood exams were performed between days 10-14. For the animals that received vincristine, vinblastine, mitoxantrone, or doxorubicin, their exams were performed between days 7-10. For the animals that received cyclophosphamide, their exams were performed on the third day of the 4-day cycle due to the development of severe neutropenia in previous cases (author experience) [Table 2]. If neutropenia (< 1,500 neutrophils) was present, the 4th dose of cyclophosphamide was not given, and supportive treatment was administered instead.

Severity grade I vomiting (despite prophylactic oral administration of antiemetics) was observed in 7 (6%) cases. Six of these cases occurred in association with cyclophosphamide, and the other case occurred in association with vincristine. Diarrhea was not reported for any of the cases examined.

Various grades of inappetence/anorexia occurred in 17 (12%) cases. Four cases were grade II, 12 cases were grade III, and 1 case was grade

Table 2. Hematological examination of cats submitted to different chemotherapeutic drugs.

Chemotherapy agent	Exams
Lomustine	Days 7 and 21
Carboplatin	Days 10-14
Vincristine	Days 7-10
Vinblastine	Days 7-10
Mitoxantrone	Days 7-10
Cyclophosphamide	Day 3 (in the 4-day cycle)

IV. Cyclophosphamide caused various grades of inappetence in 12/18 cats, including grade II (n = 1), grade III (n = 10), and grade IV (n = 1). Doxorubicin also caused grade II and grade III inappetence for 3 cats and 2 cats, respectively (Figure 1).

Neutropenia is a major side effect of chemotherapy and it was only observed in 25/112 (22%) cases. The severity of neutropenia included grade I (2/25 cases), grade II (5/25 cases), grade III (14/25 cases), and grade IV (4/25 cases). Cyclophosphamide was the chemotherapy agent responsible for most of the cases of neutropenia (14/18), and grades 1-4 had an incidence of 1 case, 2 cases, 7 cases, and 4 cases, respectively (Table 3). Carboplatin also caused neutropenia in 5/21 cats (including one case of grade I and 14 cases of grade III), as did lomustine in 5/37 cats (including 2 cases of grade II and 3 cases of grade III). Vincristine caused grade I neutropenia in 1 case, while doxorubicin, mitoxantrone, and vinblastine were not associated with any cases of neutropenia (Figure 2). Sepsis secondary to chemotherapy also did not occur in any of the animals in this study.

Thrombocytopenia was observed in 8 (7%) cases, with grades 1-3 affecting 3, 4, and 1 cats, respectively. Moreover, 4 cases were associated with cyclophosphamide, 3 cases were associated with lomustine, and 1 case involved vincristine (Figure 3).

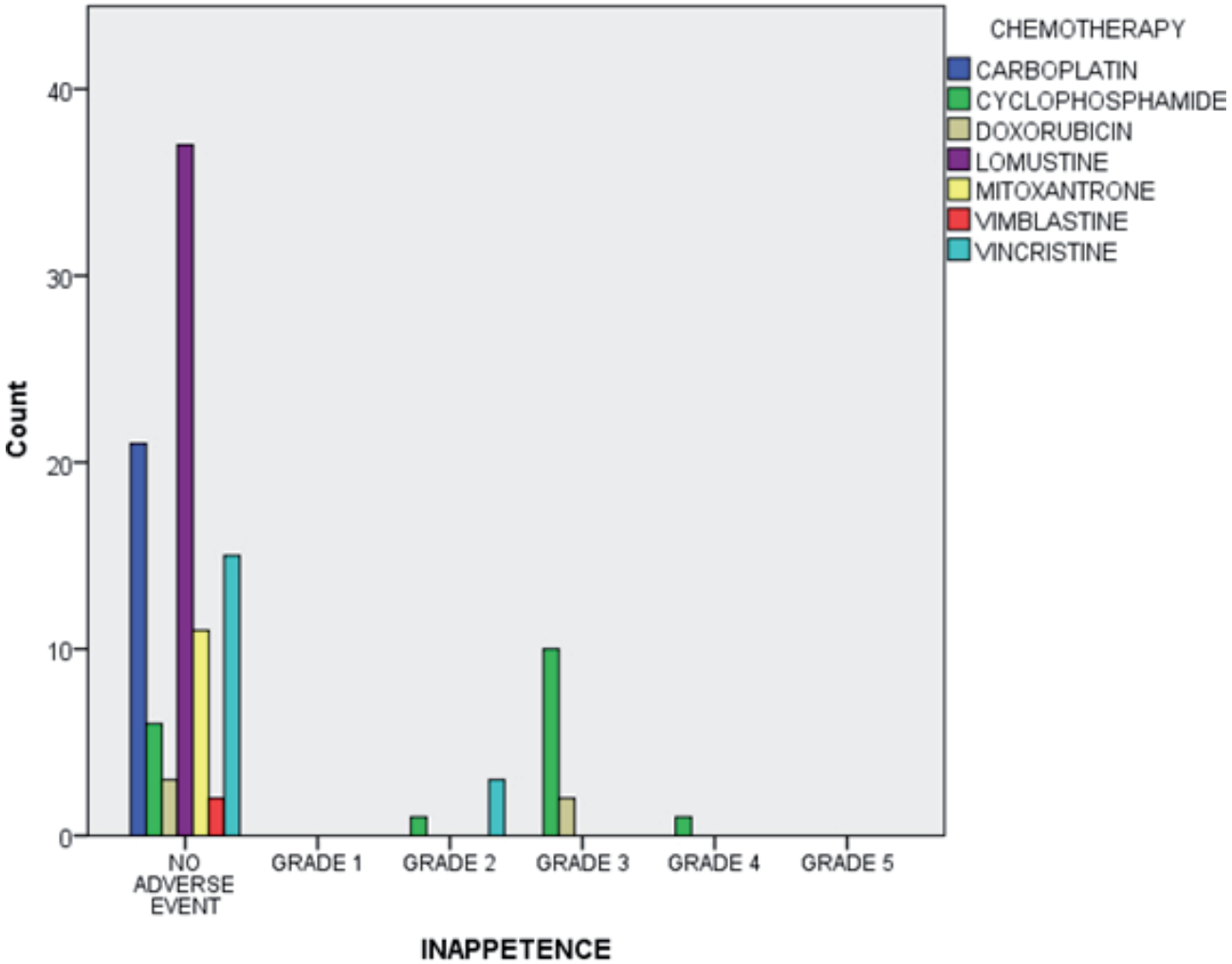

Figure 1. Incidence of inappetence according to the chemotherapy agent administered.

Table 3. Neutrophils count before and on 3rd day after cyclophosphamide administration (4-day cycle) in cats.

Cat	Age	Breed	Neutrophils before chemotherapy+	Neutrophils on 3rd day	Neutropenia Grade	Tumor	Concomitant disease
1	8	Mixed	4,012	374	Grade IV	Mediastinal Lymphoma	-
2	4	Mixed	10,582	< 500*	Grade IV	Mediastinal Lymphoma	Retrovirus
3	6	Mixed	4,680	720	Grade III	Multicentric Lymphoma	Retrovirus
4	2	Mixed	4,356	3,286	N	Mediastinal Lymphoma	Retrovirus
5	3	Mixed	6,750	1,398	Grade II	Mediastinal Lymphoma	Retrovirus
6	2	Mixed	3,540	958	Grade III	Mediastinal Lymphoma	Retrovirus
7	2	Mixed	19,845	2,430	Grade I	Mediastinal Lymphoma	Retrovirus
8	7	Mixed	3,388	3,726	N	Renal lymphoma	Retrovirus
9	3	Mixed	6,768	364	Grade IV	Mediastinal Lymphoma	Retrovirus
10	4	Mixed	2,840	484	Grade IV	Mediastinal Lymphoma	Retrovirus
11	14	Siamese	16,942	3,840	N	Gastrointestinal lymphoma	Renal disease
12	5	Siamese	8.532	814	Grade III	Spinal Lymphoma	Retrovirus
13	12	Mixed	7.519	1.478	Grade II	Nasal Lymphoma	-
14	1	Mixed	4.050	988	Grade III	Mediastinal Lymphoma	Retrovirus
15	1	Mixed	4.128	925	Grade III	Mediastinal Lymphoma	Retrovirus
16	15	Siamese	9.215	718	Grade III	Gastrointestinal lymphoma	-
17	9	Mixed	5.548	810	Grade III	Mediastinal Lymphoma	Retrovirus
18		Ragdoll	10.160	9.594	N	Mediastinal Lymphoma	-

+Normal reference range for neutrophils: 2.500-12.500 cells/µl. * Specific leucometry was not possible due to intense leucopenia. Global leucometry 800 cells/µl. N – Absence of neutropenia.

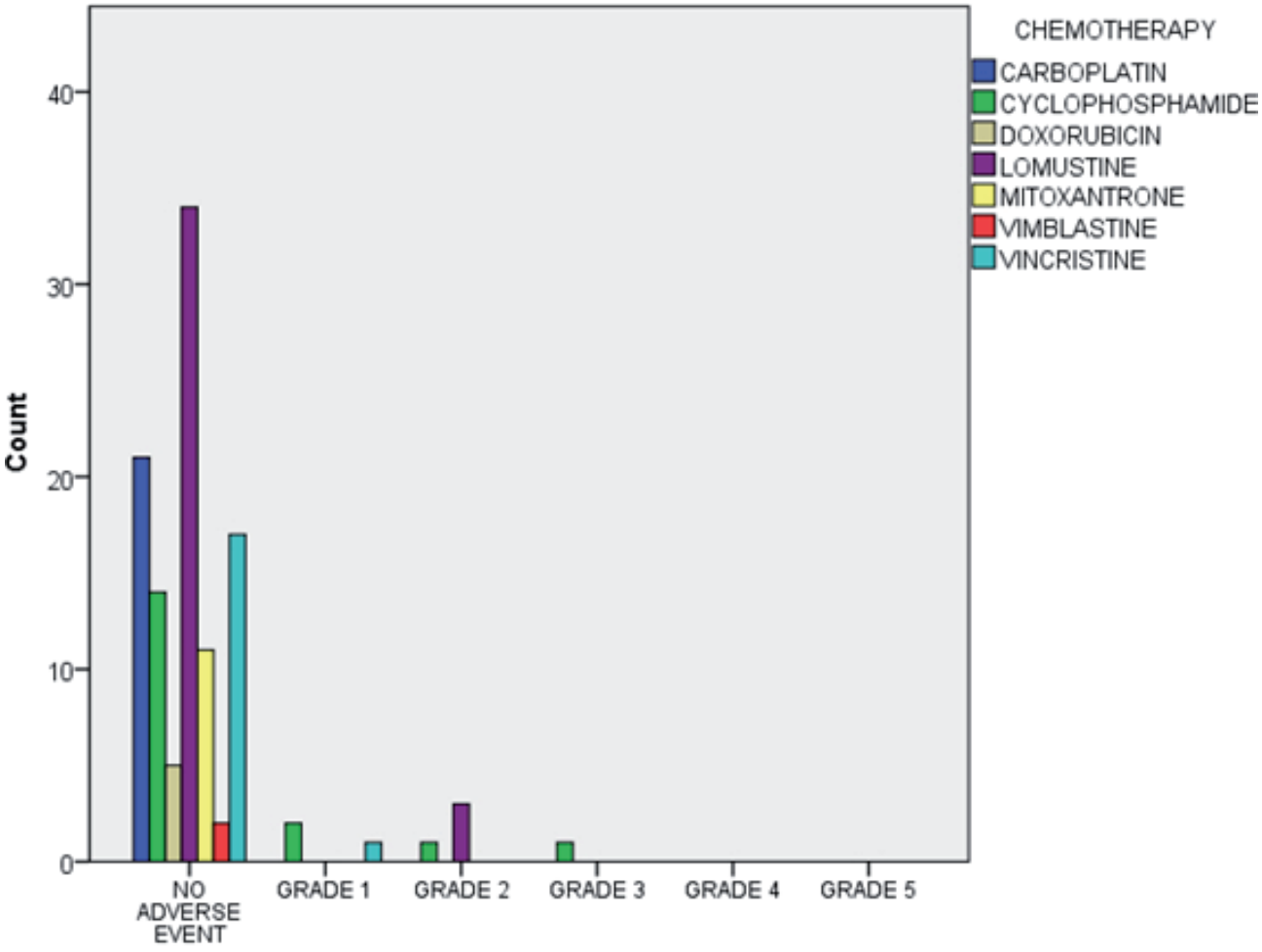

Figure 2. Incidence of neutropenia according to the chemotherapy agent administered.

Azotemia (grade III) only occurred in 1 cat following administration of doxorubicin, and this cat did not have a history of renal disease. Elevated levels of ALT and/or ALP (grade II) were also only observed in 1 cat after cyclophosphamide treatment.

According to the current VCOG-CTCAE grading system, the adverse effects of chemotherapy were grade I in 93 (83%) cases, and was grades 2-4 in 8 (7%), 9 (8%), and 2 (2%) of the other cases, respectively. Grade V adverse effects were not reported for any of the cases examined. The severity grades for the cases involving carboplatin treatment varied from 1-4, and affected 76%, 9%, 10%, and 5% of the cats, respectively. The severity grades for the cases involving cyclophosphamide treatment varied from 1-3, and affected 83%, 6%, and 11% of the cats, respectively. The severity grades for the cases involving lomustine treatment varied from grades 1-4, and affected 81%, 11%, 5%, and 3% of the cats, respectively. The severity grades for the cases involving vincristine treatment varied from grades 1-3, and affected 89%, 5.5%, and 5.5% of the cats, respectively. Finally, mitoxantrone treatment was associated with severity grades 1 and 2 in 91% and 9% of the cases, respectively (Figure 4).

A statistical association between neutropenia, vomiting, inappetence, azotemia and chemotherapeutic agent was identified for the chemotherapy agents. For example, the Kruskall-Wallis test confirmed the presence of a statistically significant difference between the chemotherapy agents and the incidences of neutropenia, vomiting, inappetence, azotemia ($P < 0.05$). To further identify these differences, the Mann-Whitney statistical test was applied. In paired comparisons, a statistical difference was observed with the administration of cyclophosphamide versus administration of the other chemotherapeutic agents. For example, cyclophosphamide was associated with more adverse events than carboplatin, leading to statistically significant neutropenia ($P < 0.001$) and

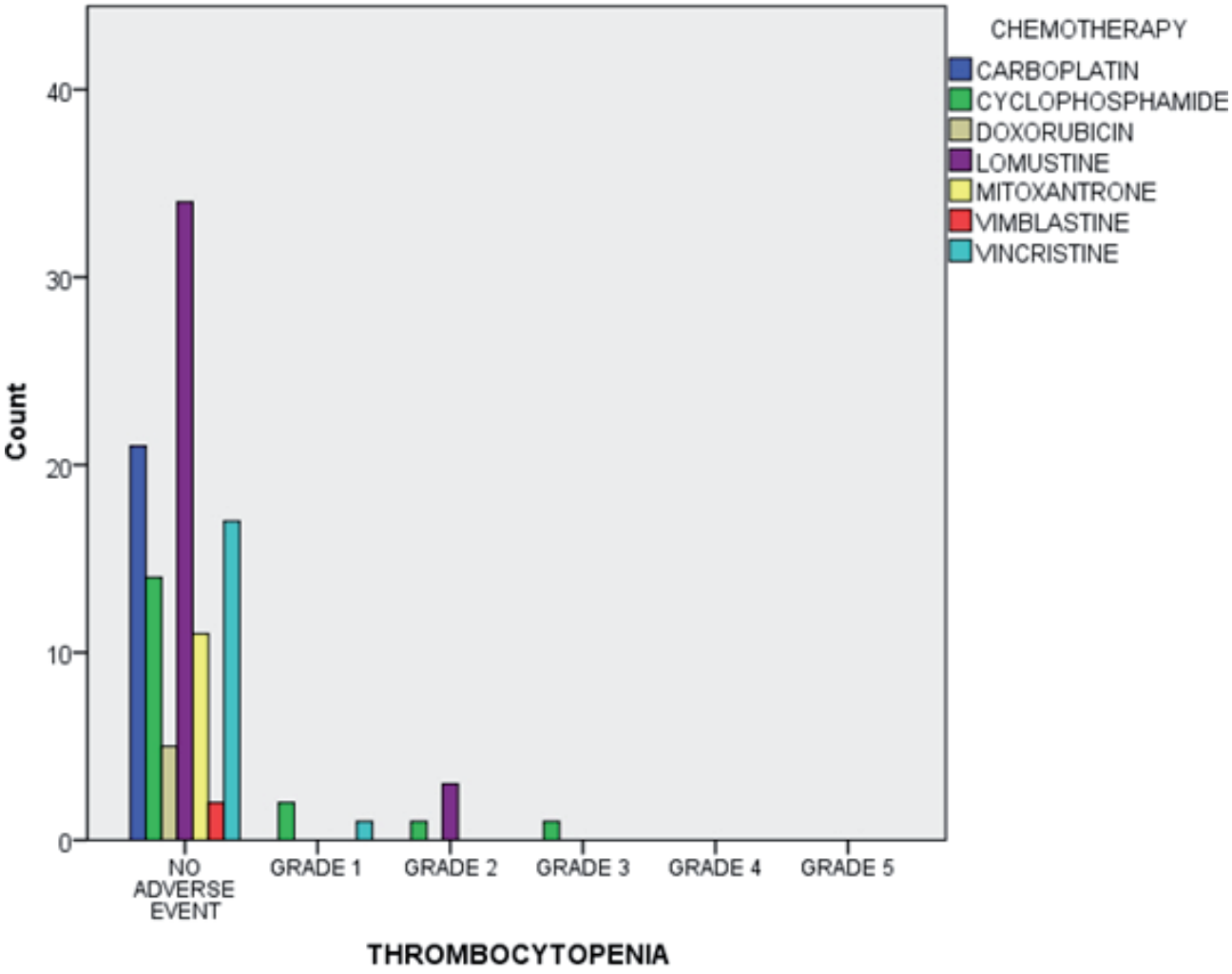

Figure 3. Incidence of thrombocytopenia according to the chemotherapy agent administered.

inappetence ($P < 0.001$). Cyclophosphamide also caused more neutropenia than doxorubicin ($P = 0.007$).

Doxorubicin was statistically associated with more inappetence when compared to lomustine ($P = 0.01$) and vincristine ($P = 0.03$). It was not possible to evaluate statistical associations between the use of vinblastine and the other chemotherapeutic agents due to the smaller number of animals that were treated with vinblastine. Furthermore, all of the other associations between the chemotherapeutic agents did not exhibit statistically significant differences in relation to the variables analyzed ($P > 0.05$).

Cyclophosphamide was associated with more adverse events when compared with the other chemotherapeutic agents in regard to neutropenia, inappetence and vomiting. In contrast, cats treated with mitoxantrone and vinblastine were associated with greater tolerance.

DISCUSSION

In general, the chemotherapy regimens in the cases examined were well tolerated. The toxicity experienced was infrequent and mostly mild, thereby resulting in satisfactory tolerability of the chemotherapy regimens. According to the current grading system for the adverse effects of chemotherapy (VCOG-CTCAE) [15], 83% of the cases examined included grade I, indicating that most of the cats experienced asymptomatic, or mild symptoms, and medical intervention was not needed. In previous studies of dogs and cats, a severe adverse event following chemotherapy was reported for fewer than 1 in 4 animals, and approximately 3-5% experienced a serious adverse event that led to hospitalization [1,2]. In the present study, 2% of the cats experienced serious or life threatening adverse events.

The only chemotherapeutic agent that was associated with inappetence, vomiting, and neutropenia was cyclophosphamide, a nitrogen mustard agent that is

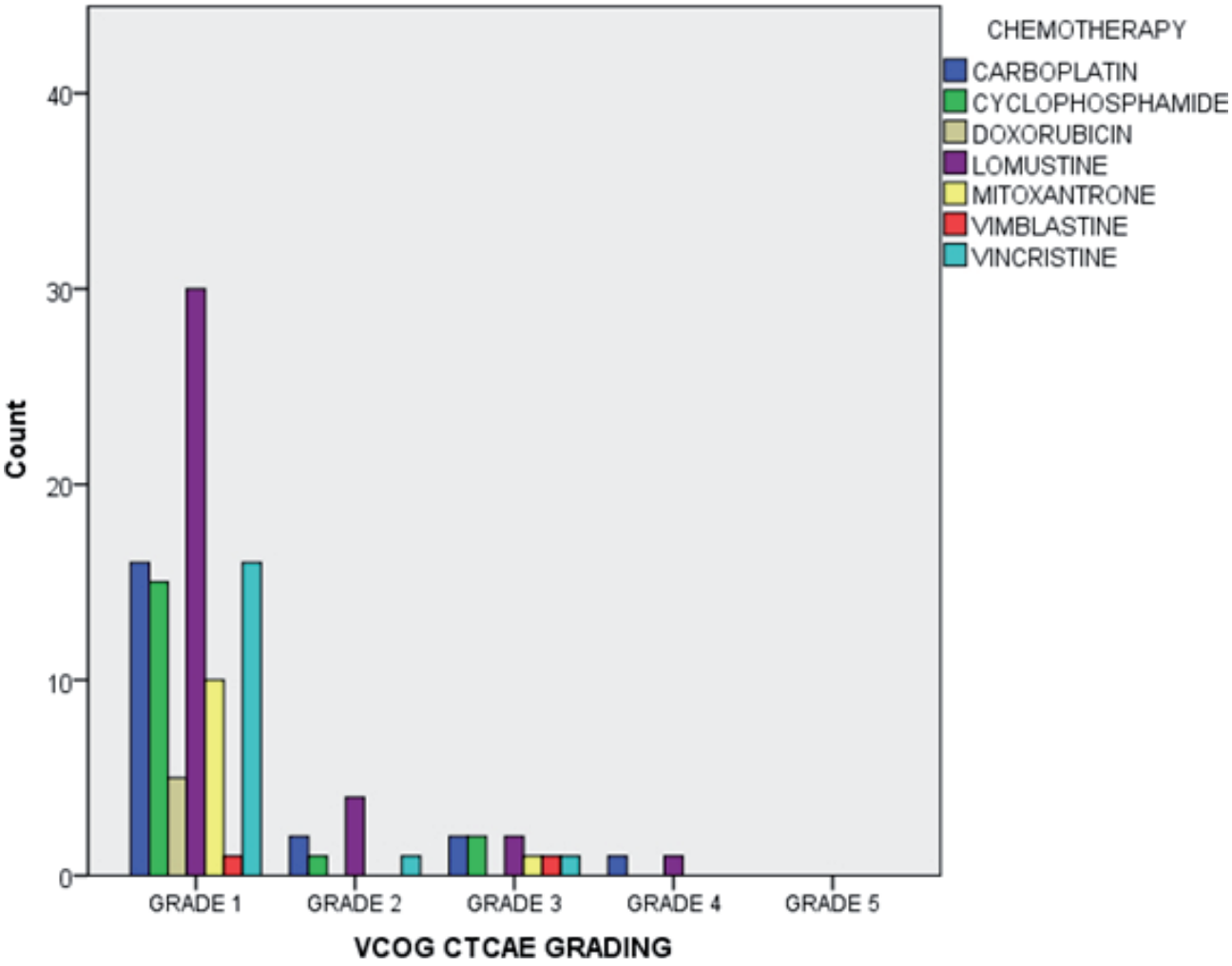

Figure 4. Grading system of adverse events to chemotherapy according to Veterinary Cooperative Oncology Group (VCOG) criteria.

commonly included in multiagent protocols for lymphoma in both dogs and cats [4]. A fractionated dosing schedule has been indicated in some protocols (e.g., 50 mg/m^2 for 3-4 consecutive days after doxorubicin or vincristine), and a similar fractionated dosing schedule was used for cyclophosphamide in the cases examined for this study. However, despite the preventive administration of an antiemetic, inappetence and nausea were observed in most of the cats that received cyclophosphamide. Vomiting was reported for 7 cats, and 6 of these cats had received cyclophosphamide. In the present study, inappetence occurred in 70% of the cats that received cyclophosphamide, and most of the conditions were severe or medically important, with supportive treatment needed. In another study of cats, side effects were reported for vincristine (38%) and doxorubicin (21%) more often than for cyclophosphamide (15%) [12]. It is possible that administration route may account for these differences in results. Additionally, cyclophosphamide was evaluated in cats receiving COP protocol, which had received vincristine 2 days before. This fact may have worsened hematological and gastrointestinal effects, as toxicity from vincristine was also associated with cyclophosphamide administration.

Doxorubicin is another chemotherapeutic agent that has been associated with gastrointestinal toxicity. In particular, vomiting and anorexia are the most commonly reported side effects of doxorubicin [11]. In the present study, all the 5 cats developed inappetence after receiving doxorubicin.

Mitoxantrone is another chemotherapeutic agent that has been associated with gastrointestinal side effects [3,10], although none of the cats of the present cohort that received mitoxantrone developed vomiting, anorexia, or diarrhea. Similarly, carboplatin has been associated with gastrointestinal side effects such as lethargy, loss of appetite, vomiting, and diarrhea [1], yet none of the studied cats developed any of these side effects.

For the cats that experienced inappetence, vomiting, and/or nausea, maropitant was administered subcutaneously together with oral administrations of ondansetron and omeprazol. These drugs provided a good antiemetic effect, as previously reported [5]. In the study by Leo *et al*. [8], a decrease in appetite and vomiting represented transitory episodes during the first 4 weeks of treatment, and these were controlled with antiemetic drugs [8].

Administration of carboplatin and vincristine led to neutropenia in a subset of the cats examined, while the administration of doxorubicin, mitoxantrone, or vinblastine was not associated with neutropenia in any of the examined cases. Administration of doxorubicin has been shown to cause neutropenia (grades 1-4) in cats, and neutropenia has been more often associated with higher doses of doxorubicin [11]. A dose of 1 mg/kg was used in the cases examined, and this dose has been associated with a reduced incidence of neutropenia compared with a dose of 25 mg/m^2 [11]. Differences in the administered doses of doxorubicin may explain the absence of neutropenia in the cases examined.

The administration of vinblastine was not associated with neutropenia in the present cohort, although the administration of vinblastine and vincristine were previously associated with neutropenia in cats [6]. Furthermore, neutropenia has been associated with vinblastine more often than vincristine [6]. This observation was not made in the present study, although the doses applied for the 2 drugs were higher than previously described [6]. It is possible that the use of different protocols to treat cats with cancer may be a contributing factor to this result.

According to Vail [14], neutropenia is likely to be observed 7-10 days after the administration of most chemotherapy drugs. Exceptions to this rule include vinblastine and paclitaxel, which can cause neutropenia as early as 4-5 days after the administration; and carboplatin which can occasionally cause neutropenia as late as 2-3 weeks after administration [4]. However, in the present study, 22% of the cats that received cyclophosphamide developed severe cases of neutropenia by the third day of the fractionated dosing schedule that was designed to extend over 4 consecutive days (50 mg/m^2). This result differed from that reported by Leo *et al.* [8] where oral treatment with cyclophosphamide did not result in neutropenia. Moreover, the dose used in the cases examined (200 mg/m^2) was higher than the dose used by Leo *et al.* [8] (metronomic 66 mg/m^2 weekly). Thus, it appears that the incidence of neutropenia may be dependent on the dose of the chemotherapeutic agent that is applied. Additionally, the high number of cats with neutropenia following cyclophosphamide administration in the present study may be associated with the retroviral status. All cats treated with this chemotherapeutic agent had lymphoma, and 13/18 of them had FeLV and/or FIV, which may have worsened myelosuppression.

Most companion animals have a low risk of infection if their neutrophil count remains greater than 1000/ L. However, the severity of neutropenia and associated sepsis can be extremely variable, ranging from clinically silent to overwhelming and fatal [14]. Sepsis did not occur in any of the cats of the present cohort, yet it could have developed if hematology was not performed on the 3rd day of each chemotherapy regimen. The present results also demonstrate that cats (especially those with retroviral diseases) appear to be particularly susceptible to cyclophosphamide--associated toxicities. Thus, cyclophosphamide should be used with caution for the treatment of cancer in cats, and the development of inappetence, vomiting, and neutropenia should be closely monitored.

Azotemia (grade III) occurred in only one cat following administration of doxorubicin, and this cat did not have a history of renal disease. Generally, doxorubicin chemotherapy is avoided in cats that have a history of renal disease due to the known nephrotoxic properties of doxorubicin [11], and mitoxantrone is often administered instead. In the present study, the administration of mitoxantrone in cats with evidence of renal disease may explain the low incidence of azotemia. Renal damage was still a possible side effect following mitoxantrone, as in another study, some cats developed azotemia with this drug [3]. In previous literature, renal toxicity has also been reported to occur in cats following the administration of cyclophosphamide [8]. However, renal damage was not reported in the cases examined involving cyclophosphamide in the present study.

Lomustine has been shown to cause severe hepatotoxicity in dogs [7]. Moreover, lomustine-induced liver injury or hepatoxicity is often suspected when increased activities of ALT and ALP are detected days to weeks after the administration of lomustine. In a study by Musser *et al*. [9], only 2/29 cats exhibited increased ALT activity above the reference interval

one month after their treatment with lomustine. Correspondingly, clinically significant hepatic injury has been found to be generally uncommon in cats that receive lomustine [9]. In the present study, increased ALT activity was not detected in any of the cats that received lomustine up to 21 days after their treatments.

In a previous study of owners' perceptions about chemotherapy in dogs and cats, 62/69 owners thought that the anticancer chemotherapy regimens received were generally worthwhile, although only 10 cats were included in this study. Furthermore, the most common side effects were hair loss, weight loss, and weakness, all of which affected 5/10 of the cats [2]. Among these effects, weight loss was the most severe.

This result may encourage veterinarians to administer chemotherapy to feline patients, with the exception being cyclophosphamide chemotherapy which was associated to more adverse events. In a previous study of owners' perceptions of their cats' quality of life during the administration of cyclophosphamide, vincristine sulfate, and prednisone (COP chemotherapy) for lymphoma, adverse effects were experienced by 27/31 (87%) cats [13].

CONCLUSION

For the cases examined, the chemotherapy regimens administered were very well tolerated. The most common adverse events were neutropenia, inappetence, thrombocytopenia and vomiting. The present results also indicate that cyclophosphamide should be used with caution in cats, especially those with retroviral diseases, and that adequate antiemetic and nutritional support should be available if needed. In addition, febrile neutropenia/sepsis may be avoided by using a fractionated schedule and performing hematologic exams on the third day of treatment. If neutropenia does develop, interruption of treatment and administration of supportive treatment should be provided. Vincristine was associated with mild toxicities, and carboplatin, mitoxantrone, lomustine, and vinblastine were very well tolerated. Thus, the present results demonstrate that chemotherapy can be well tolerated by cats and it represents a safe treatment for cancer when it is properly monitored.

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