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Chemotherapy-induced neutropenia is associated with prolonged remission duration and survival time in canine lymphoma

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ABSTRACT

Myelosuppression is one of the most common side effects of chemotherapy. The aim of this study was to determine whether chemotherapy-induced neutropenia is a positive prognostic indicator for remission and survival time in dogs with lymphoma. Fifty dogs with multicentric lymphoma received CHOP-based (C-cyclophosphamide; H-hydroxydaunorubicin; O-vincristine; P-prednisolone) chemotherapy using conventional dosages. Complete blood counts were recorded to determine the presence or absence of neutropenia after treatment. Toxicity, remission, and survival times were recorded and analysed.

Thirteen dogs had chemotherapy-induced neutropenia and 37 had no neutropenia during the study period. No statistical difference was found between the groups for signalment or the presence of historical negative prognostic factors, except for bodyweight ($P = 0.02$). The median first remission times in the neutropenia and no neutropenia groups were 812 and 219 days, respectively ($P < 0.01$). The median survival times of dogs in the neutropenia and no neutropenia groups were 952 and 282 days, respectively ($P < 0.01$). Dogs with lymphoma that had chemotherapy-induced neutropenia exhibited significantly increased remission and survival times compared with dogs without neutropenia. Chemotherapeutic dosages may be adjusted individually to induce neutropenia without severe adverse effects in order to achieve longer remission and survival times.

Introduction

The annual incidence of lymphoma, which is the most common haematopoietic neoplasm in dogs, is reported to be 114/100,000 dogs (Dobson et al., 2002). Lymphoma accounts for approximately 7–24% of all canine neoplasias and 83% of all canine haematopoietic malignancies (Kaiser, 1981; Moulton and Harvey, 1990). Numerous chemotherapeutic protocols for treating canine lymphoma have been developed over the past 40 years including the multiagent CHOP-based (C-cyclophosphamide; H-hydroxydaunorubicin; O-vincristine; P-prednisolone) protocol, and complete remission rates of 73–92% with median first remission duration (FRD) ranging from 8 to 12 months have been reported (Garrett et al., 2002; Rassnick et al., 2007; Burton et al., 2013; Mutz et al., 2013).

Several negative prognostic factors in dogs with lymphoma have been reported, including T cell lymphoma, Stage V, Substage b, hypercalcaemia, anaemia, cranial mediastinal lymphadenopathy, high proliferation index, and pretreatment with corticosteroids (Teske et al., 1994; Abbo and Lucroy, 2007; Miller et al., 2009; Marconato et al., 2011). Nearly all of these prognostic factors are evaluated at diagnosis and before treatment. Prognostic indicators after chemotherapy have not been widely reported.

Chemotherapy can prevent cellular replication and induce apoptosis by damaging DNA. Because actively dividing cells are sensitive to DNA damage, chemotherapy is effective against rapidly growing neoplasms. Other rapidly dividing cells, such as bone marrow stem cells, are also damaged by chemotherapeutic drugs resulting in myelosuppression, which is one of the most common side effects of chemotherapy. Because cells with the shortest life spans are most susceptible, myelosuppression commonly manifests as a decrease in neutrophil count.

Human studies have indicated that chemotherapy-induced neutropenia is positively correlated with patient outcomes for various solid tumours. Tewari et al. (2014) found that chemotherapy-induced neutropenia was associated with improved survival in primary advanced ovarian cancer and in peritoneal carcinoma patients treated with carboplatin-plus-paclitaxel chemotherapy. Similar outcomes have been reported for non-small cell lung cancer (Di Maio et al., 2005), breast cancer (Koutras et al., 2008), gastric cancer (Shitara et al., 2010), and colorectal cancer (Shitara et al., 2009) patients.

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Few studies on chemotherapy-induced neutropenia and cancer have been published in the veterinary literature. Based on our research, only three reports have indicated increased remission duration or survival time (ST) in dogs with lymphoma that required dose reduction and treatment delays after being treated with chemoradiotherapy or dose-intensified chemotherapy protocols (Vaughan et al., 2007; Sorenmo et al., 2010; Burton et al., 2013). However, no studies have investigated the effects of chemotherapy-induced neutropenia in dogs with lymphoma treated with conventional dosages of chemotherapy.

The aim of this prospective study was to evaluate the correlation between chemotherapy-induced neutropenia and response, FRD, and overall ST in CHOP-based chemotherapy for canine lymphoma.

Materials and methods

Patient selection and evaluation

Dogs with histopathologically or cytologically diagnosed lymphoma were treated with CHOP-based chemotherapy (Table 1) at the National Taiwan University Veterinary Hospital from June 2006 to March 2014. Dogs with multicentric lymphoma that had received at least two doses of doxorubicin were included in the study. Dogs with other concurrent diseases and those that had received chemotherapeutic drugs or corticosteroids before diagnosis were excluded.

We collected data on breed, sex and neuter status, age, bodyweight, immunophenotype, clinical stage and substage, complete blood count (CBC) before and after chemotherapy, calcium concentration, chemotherapy protocol, treatment response, dates of therapy start, final follow-up, and death.

CBCs were measured after every chemotherapy session, which was 1 week after vincristine or cyclophosphamide administration, or 2 weeks after doxorubicin administration. We obtained data over the first 11 weeks because most CHOP-based protocols are initiated by vincristine administration at weeks 1, 3, 6, and 8; cyclophosphamide administration at weeks 2 and 7; doxorubicin administration at weeks 4 and 9, and prednisolone administration within the first 4 weeks at a tapered dosage.

Dogs with a neutrophil count <3000/μL were considered to have neutropenia. Those in the ranges of 1500–2999/μL, 1000–1499/μL, 500–999/μL, and < 500/μL were classified as Grades 1, 2, 3, and 4 neutropenia, respectively. When blood examination before chemotherapy revealed any grade of neutropenia, treatment was delayed and the dog was re-evaluated the following week. Neutropenic episodes and their grades were recorded for each animal.

Gastrointestinal toxicity after each chemotherapy session was also recorded for dogs and graded 1–5 according to the veterinary cooperative oncology group – common terminology criteria for adverse events (Veterinary Cooperative Oncology Group, 2011).

Response assessment

Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0) (Vail et al., 2010) were applied to evaluate the therapeutic response. A complete response (CR) was characterised by the disappearance of all measurable diseases; a partial response (PR) was characterised by a decrease (>30% but < 100%) in the mean-sum longest diameter of target lesions; stable disease (SD) was characterised by a <30% decrease or <20% increase in target lesions compared to baseline; and progressive disease (PD) was characterised by a >20% increase in target lesions or the development of a new lesion.

The FRD was defined as the time from achieving remission until disease progression. The ST was calculated from the time of diagnosis to patient death. Dogs were censored in remission duration analysis for the following reasons: (1) relapse had not occurred before the end of the study period; (2) loss to follow-up, or (3) death before relapse. Dogs were censored in survival analysis for the following reasons: (1) loss to follow-up; (2) death from causes other than lymphoma, or (3) they were still alive. The follow-up evaluation interval was once monthly during first 3 months, and then every 3 months. The owners were informed so they could visit the clinic when disease progression was reported.

Table 1
First 9 weeks of CHOP-based chemotherapy for canine lymphoma.

	Week								
	1	2	3	4	5	6	7	8	9
Vincristine (0.7 mg/m^2 IV)	●		●			●		●	
Cyclophosphamide (250 mg/m^2 PO)		●					●		
Doxorubicin (30 mg/m^2 IV)				●					●
Prednisolone (mg/kg, PO daily)	2.0	1.5	1.0	0.5					

CHOP, cyclophosphamide (C), hydroxydaunorubicin (H), vincristine (O), and prednisolone (P); IV, intravenous; PO, per os.

Statistical analysis

Comparisons between continuous variables (age and bodyweight) were made using Student's *t* test. We compared sex between two groups using a paired *t* test. The proportion of dogs in each group with known prognostic factors (i.e. clinical stage, substage, immunophenotype, and hypercalcaemia), the proportion of dogs showing signs of toxicity, and their responses were compared using Fisher's exact test. The median FRD and ST were determined with a Kaplan–Meier analysis, and the differences between the two groups were assessed using the log-rank test. All statistical analyses were considered significant at $P < 0.05$.

Results

Fifty canine lymphoma patients were included in the study. Blood examinations revealed that 13/37 dogs had chemotherapy-induced neutropenia. The patients' signalment, clinical stage and substage, and immunophenotype are listed in Table 2. Most dogs in this study were of mixed breed ($n = 16$), followed by Golden retrievers ($n = 13$), Beagles ($n = 6$), Shih Tzus ($n = 2$), Maltese ($n = 2$), Bull terriers ($n = 2$), and one each of Chihuahua, Bichon, Dachshund, Schnauzer, Welsh corgi, Labrador retriever, Pug, Yorkshire terrier, and Rottweiler.

The ages (mean ± SD) of the dogs in the neutropenia and no neutropenia groups were 8.2 ± 2.7 years and 6.6 ± 2.7 years, respectively, and the mean bodyweights of the dogs in the neutropenia and no neutropenia groups were 13.7 ± 7.9 kg and 23.3 ± 13.1 kg. There were nine females (two intact) and four males (three intact) in the neutropenia group and 14 females (five intact) and 23 males (15 intact) in the no neutropenia group. The mean bodyweight of the neutropenia group was significantly less than the no neutropenia group ($P = 0.02$). There were no significant differences in the age ($P = 0.15$), sex ($P = 0.06$), stage ($P = 0.31$) or substage ($P = 0.16$) between the two groups. Only 8 and 20 dogs in the neutropenia and no neutropenia groups, respectively, were examined for immunophenotyping (flow cytometry or immunohistochemistry), revealing no significant differences ($P = 0.99$). No hypercalcaemic patients were included in this study (Table 2).

Twenty-six neutropenic episodes were recorded. Thirteen were related to vincristine administration (10 Grade 1, 2 Grade 2, and 1 Grade 3). Ten episodes were related to cyclophosphamide administration (10 Grade 1). Three episodes were related to doxorubicin administration (1 Grade 1 and 2 Grade 2).

Eleven dogs in the neutropenia group showed signs of gastrointestinal toxicity (Table 3). Nine were anorexic, eight had diarrhoea, and seven vomited. Fifteen (94%) episodes of Grade 1 and one (6%) of Grade 2 anorexia were recorded. Thirteen (100%) episodes of Grade 1 diarrhoea were observed. Sixteen (84%) episodes of Grade 1, two (11%) of Grade 2, and one (5%) of Grade 3 vomiting were recorded.

Table 2
Comparison of signalment and negative prognostic factors between neutropenia and no neutropenia groups.

	Neutropenia ($n = 13$)	No neutropenia ($n = 37$)	*P* value
Age (years)	8.2	6.6	0.15[a]
Bodyweight (kg)	13.7	23.3	0.02[a]
Sex			
Female	9 (69%)	14 (38%)	0.06[b]
Male	4 (31%)	23 (62%)	
Clinical stage			
V	0 (0%)	6 (16%)	0.31[c]
Substage			
b	0 (0%)	7 (19%)	0.16[c]
T cell	0 (0%, 0/8)	1 (5%, 1/20)	0.99[c]
Hypercalcaemia	0 (0%)	0 (0%)	1.00[c]

[a] Student's *t* test.
[b] Paired *t* test.
[c] Fisher's exact test.