수의학석사 학위논문

A retrospective study of multicentric lymphoma treated with CHOP in small breed dogs

소형견에서 CHOP로 치료를 받은 다중심성 림프종 환자에 대한 후향적 연구

2021년 2월

서울대학교 대학원

수의학과 임상수의학(수의내과학) 전공

김 태 희

A retrospective study of multicentric lymphoma treated with CHOP in small breed dogs

소형견에서 CHOP로 치료를 받은 다중심성 림프종 환자에 대한 후향적 연구

지도교수 윤 화 영

이 논문을 수의학 석사 학위논문으로 제출함

2020년 10월

서울대학교 대학원

수의학과 임상수의학(수의내과학) 전공

김 태 희

김태희의 석사 학위논문을 인준함

2021년 1월

위 원 장 김 용 백 (인)

부 위 원 장 윤 화 영 (인)

위 원 채 준 석 (인)

Abstract

A retrospective study of multicentric lymphoma treated with CHOP in small breed dogs

TAE-HEE KIM

Supervised by Prof. Hwa-Young Youn

Division of Clinical Veterinary Medicine (Veterinary Internal Medicine)

Department of Veterinary Medicine

The Graduate School of Seoul National University

Lymphoma is one of the most common malignant tumors in dogs. Combination chemotherapy with vincristine, cyclophosphamide, doxorubicin and prednisolone (CHOP) is the most effective treatment for multicentric lymphoma. Previous studies have evaluated the response of large dogs to CHOP treatment and identified prognostic factors; however, studies on small dogs are lacking. In this study, we investigated the outcomes and prognostic factors for multicentric lymphoma treated with CHOP in small breed dogs. Dogs, weighing under 15 kg, that were diagnosed with multicentric lymphoma and treated with CHOP between 2014 and 2020 were included in this study. The responses of patients to CHOP treatment were assessed.

Of 38 patients, 54.3% were evaluated as being in complete remission (CR),

31.4% in partial remission (PR), and 14.3% in no remission (NR). The overall response rate was 85.7%. The mean survival time (MST) of all patients was 490.6 ± 474.5 days. MSTs for CR, PR, and NR patients were 666.9 ± 436.7, 297.2 ± 263.3, and 170.8 ± 136.0 days, respectively which were significantly longer for the CR group than those for the PR (p=0.029) and NR (p=0.027) groups. Among the CR patients, MST was longer under the following conditions: age under 10 years (p=0.011), no cardiovascular heart disease (CVHD) (p=0.002), and no history of hospitalization due to side effects from chemotherapy (p=0.031).

Response to CHOP treatment acts as an important prognostic factor. Furthermore, age, presence of CVHD, and hospitalization due to side effects from chemotherapy are important prognostic factors within the CR group. These results will be beneficial for confirming outcome information and explaining the best treatment and prognosis.

Keywords: Lymphoma, Small-breed dogs, Survival time, Prognostic factors

***Student Number*: 2019-21265**

CONTENTS

List of Figures

List of Tables

ABBREIVATIONS

ANOVA	Analyzed using one-way analysis of variance
BUN	Blood urea nitrogen
CBC	Complete blood count
CHOP	Cyclophosphamide, vincristine, doxorubicin and prednisolone
CR	Complete remission
CVHD	Cardiovascular heart disease
FACS	Fluorescence activated cell scanning
FNA	Fine needle aspiration
GI	Gastrointestinal
HSE	Hospitalizing side effect
LAH	Local animal hospital
LD	Long diameter
MST	Mean survival time
NR	No remission
PARR	Polymerase chain reaction for antigen receptor rearrangements
PCV	Packed cell volume
PD	Progressive disease
PDS	Prednisolone

PR	Partial remission
SD	Stable disease
S.D.	Standard deviation
VMTH SNU	Veterinary Medical Teaching Hospital of Seoul National University
WBC	White blood cell

1. Introduction

Lymphoma is one of the most common tumors, accounting for 83% of hematopoietic neoplasia in dogs and comprises 7–24 % of all tumors (Vail et al., 2019, Zandvliet, 2016). Lymphoma is caused by the abnormal proliferation of malignant lymphoid cells and occurs mainly in lymphoid tissues such as the lymph nodes and spleen (Mortier et al., 2012). Lymphomas are classified as multicentric, alimentary, mediastinal, and such, depending on the anatomical location; of these, multicentric lymphoma accounts for 80% of all cases. Although the etiology of lymphoma is not well known, infectious, genetic, environmental and immunological factors are associated with prevalence (Zandvliet, 2016, Vail et al., 2019, Mortier et al., 2012).

CHOP (C=cyclophosphamide; H=hydroxydaunorubicin; O=oncovin; P=prednisolone) is one of the most recommended chemotherapy treatments for lymphoma (Vail et al., 2019, Chun, 2009). Without treatment, patient life expectancy is 4–6 weeks, but most patients administered the CHOP protocol show a positive response and have a survival time of 10–14 months (Mortier et al., 2012, Sorenmo et al., 2010, Vail et al., 2019). Many studies have examined the therapeutic response and prognostic factors of patients treated with CHOP. Through these studies, stage, substage, immunophenotype and the presence of hematological abnormalities (anemia or thrombocytopenia) and chronic inflammation have been identified as prognostic factors (Kiupel et al., 1999, Sorenmo et al., 2010, Childress et al., 2018, Jagielski et al., 2002, Miller et al., 2009, Baskin et al., 2000).

Morphological and physiological differences exist among breeds of dog, resulting in differences in metabolic rate and lifespan (Kirkwood, 1985). Most previous studies of the CHOP protocol in dogs have focused on large breeds such as boxer, shepherd, and retriever. An assessment of treatment response in small breed dogs is lacking. Additionally, few studies have been conducted on changes in survival time due to the presence of other diseases. Underlying conditions can affect the metabolism and secretion of chemotherapy drugs. It is useful, therefore, to evaluate the effects of underlying diseases such as cardiovascular heart disease (CVHD), hormonal abnormality (such as hyperadrenocorticism) and liver failure on prognosis (Olson et al., 1990, Feldman, 2004).

The aim of this study was to evaluate the outcomes and prognostic factors in multicentric lymphoma patients who were administered the CHOP protocol, focusing on small breed dogs weighing under 15 kg.

2. Materials and Methods

2.1. Study population

Medical data for all patients diagnosed with lymphoma at Veterinary Medical Teaching Hospital of Seoul National University (VMTH SNU) between January 1, 2014 and September 1, 2020 was reviewed. Patient information was reviewed using an electronic charting program (E-friends; Pet Network Veterinarian, Seoul, Korea).

2.2. Inclusion and exclusion criteria

Small-breed dogs, weighing under 15 kg (Cherrone et al., 2004), that were diagnosed with multicentric lymphoma based on clinical signs, physical examination, blood analysis, imaging, and fine needle aspiration (FNA) of lymph nodes were included in this study. Seventy-four patients were identified of which 14 were not treated by aggressive or induction phase, but by metronomic chemotherapy. In addition, 17 dogs did not receive any treatment and no follow-up was available for 5 dogs. Thirty-eight dogs were included in the analysis.

2.3. Medical records

Patient information (breed, sex, and age), medical history, and concurrent disease were collected from the owner and recorded in the e-chart. We examined

each patient's general status, including body weight, vital signs (blood pressure, heart rate, respiratory rate, and temperature), and any abnormal findings from head to tail. All body surface lymph nodes were palpated and if any were noticeably enlarged, we measured them with calipers. Blood analysis, including complete blood count, serum chemistry, and electrolytes, was conducted. Abdominal and thoracic radiographs and abdominal ultrasound were performed to examine intraperitoneal lymph nodes and metastasis. If enlarged intraperitoneal lymph nodes or abnormal nodules were found in the liver or spleen during abdominal ultrasound, additional ultrasound guided FNA was performed for staging patients.

The stage and substage of patients were determined using the world health organization clinical staging criteria for lymphoma in domestic animals. According to the criteria, infiltration of abnormal lymphoid cells to liver, spleen, or bone marrow was crucial consideration for determining stage. However, Assessment of the liver, spleen, or bone marrow with FNA or biopsy was not performed for all patients. Though ultrasonographic findings such as "honeycomb sings" in spleen or liver could be considered as an evidence of infiltration, without FNA or biopsy, had a high portion of false-negative and false-positive (Crabtree et al., 2010). Because of these reasons, though patients had abnormal morphologies in their spleen, liver or both, they were considered as stage 3. On the other hands, abnormalities of peripheral blood such as leukocytosis, lymphocytosis, thrombocytopenia, and findings that were moderate to large lymphocyte in the blood smear were strongly suspected to determine stage 5, without bone marrow biopsy (Martini et al., 2015). Immunophenotype was determined by fluorescence activated cell scanning (FACS) or polymerase chain reaction for antigen receptor rearrangements (PARR). Patients

that were diagnosed with lymphoma at a local animal hospital (LAH) and transferred to VMTH SNU were evaluated using the same methods, based on the medical records received from LAH.

2.4. CHOP or L-CHOP protocol

The CHOP protocol includes administration of cyclophosphamide, doxorubicin, vincristine, and prednisolone (PDS); L-asparaginase was added in the L-CHOP protocol. For the first four weeks of the induction phase, vincristine (0.5–0.7 mg/m^2, weeks 1 and 3; vincristine sulfate injection, Hospira Australia Pty Ltd, Australia), cyclophosphamide (250 mg/m^2, week 2; Endoxan, Baxter Oncology GmbH, Germany), and doxorubicin (1 mg/kg, week 4; Adriamycin, Pfizer, Italy) were administered intravenously. For the L-CHOP protocol, L-asparaginase (400 U/kg; Leunase injection, Nipro Pharma Corporation, Japan) was administered subcutaneously in the first week of the protocol. At the same time, PDS (Solondo, Yuhan Corp., Seoul, Korea) was administered orally, with the dose tapering gradually from 40 mg/m^2 to 10 mg/m^2 at weekly intervals. After a week of rest, the treatment was repeated from week six, without oral PDS administration. The maintenance phase then followed. The injection interval was extended by two weeks and it took 25 weeks to finish the entire protocol. The exact dosage and schedule are shown in Table 1.

2.5. Evaluation of Response

All patients were classified using the following categories: complete remission (CR), no evidence of disease in any lymph nodes, including normalization of size (under 10 mm); partial remission (PR), sum of the long diameter (LD) of enlarged lymph nodes decreased by more than 30% compared to that before chemotherapy; progressive disease (PD), the sum of LD increased by more than 20% or new lesions appeared. Stable disease (SD) did not belong to any of the other three categories (CR, PR, or PD). We considered SD and PD together as no remission (NR). The time from assessment of response to relapse or progression was defined as the response duration and it was evaluated only in CR and PR patients. Survival time was the time from diagnosis to death. If patients were still alive as on September 1, 2020, the survival time was the duration from diagnosis to that date. Evaluation of the survival time of each patient was based on the e-chart but if medical records were omitted, we called the client and took new information over the phone.

2.6. Statistical analysis

GraphPad prism (version 6.01) software (GraphPad, Inc., La Jolla, CA, USA) was used for statistical analysis. Differences between two groups were analyzed using Student's *t*-test and differences between more than two groups were analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni multiple comparison test. Comparison of survival curves were analyzed using log-rank (Mantel-Cox) test. The results are presented as mean ± standard deviation (S.D.). Differences with a value of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Study animals

Overall information of all patients who were included in this study is shown in Table 2. The mean age of patients was 9.8 ± 3.0 years (range, 2–15 years) and mean weight was 6.4 ± 3.1 kg (range, 2.3–15.0 kg). The percentage of females [intact (n = 4, 10.5%) and neutered (n = 18, 47.4%); total (n = 22, 57.9%)] was slightly higher than that of males [intact (n = 3, 7.9%) and neutered (n = 13, 34.2%); total (n = 16, 42.1%)] (Table 3). The sum of neutered patients was higher than that of intact ones, but this was thought to be due to the high proportion of neutered patients among the patients who visited. MST according to sex is shown in Table 4 and there were no statistical differences about prevalence and MST according to sex. Shih-tzu was the most frequently affected breed (n = 11, 28.9%), followed by Maltese (n = 7, 18.4%) and Cocker spaniel (n = 4, 10.5%). Poodle, Miniature pincher, Yorkshire terrier and mongrel occupied 5.3% individually and each of the eight breeds had only one patient (Table 5).

3.2. Clinical staging and laboratory findings

Twenty-one patients (55.3%) were stage 3 (eighteen were substage a and three are substage b), twelve patients (31.6%) were stage 4 (substage a and b were six, respectively), and five patients (13.2%) were stage 5 (two were substage a and three

are substage b) (Table 6).

Except one patient which was diagnosed at LAH and was lost blood analysis results, thirty-seven patients were assessed complete blood count (CBC). Mean of white blood cell (WBC) was 15,257.8 ± 9,295.5/μl, mean of packed cell volume (PCV) was 38.6 ± 7.6%, and mean of platelet count was 28.6 ± 16.7 × 10^4/μl (Table 7). PCV and platelet count had no statistically significant difference according to the stage, however, mean WBC count of stage 5 patients was significantly higher than that of stage 3 and 4 patients (p=0.002). Especially, among five patients who categorized stage 5, two patients had high portion of lymphocyte over 70 percent (74% and 75%, respectively). Pre-treatment blood analysis including serum chemistry and electrolyte was also conducted. Patients were classified by their blood analysis results and number of patients according to classifications is shown in Table 8. Additionally, mean and S.D. values of each serum chemistry items are explained in Table 9. Among serum chemistry profiles, blood urea nitrogen (BUN) was statistically significantly low in stage 4 patients (p=0.028). There were no statistical differences about serum sodium or potassium level, according to the stage.

Among thirty-eight patients, thirty-one patients were assessed about their immunophenotype. Nine patients were assessed by FACS and nineteen patients were done by PARR. Three patients were assessed in LAH and the method was unknown. Twenty-seven patients (71.1%) were B cell type, and four patients (10.5 %) were T cell type. Seven patients were not assessed about immunophenotype (Table 10).

3.3. Correlation between survival time and characteristics of

patients at diagnosis

We compared the MST by classification according to the results of the blood analysis at diagnosis. There was no correlation between abnormalities of blood analysis and MST. Survival time according to the stages was shown in Figure 1 A and survival time according to the immunophenotype was shown in Figure 1 B. There was no significant difference in survival time among stages, substages and immunophenotypes, too.

3.4. Response to CHOP protocol

The MST of all patients was 490.6 ± 474.5 days and 54.3% (19/35) of patients were evaluated as CR; 31.4% (11/35) were PR; 14.3% (5/35) were NR; 85.7% (30/35) of the total belonged to the CR and PR groups. We could not evaluate the responses of three patients because the follow-up information was lost. MST was 666.9 ± 436.7 days (range 85–1,496 days) in the CR group, 297.2 ± 263.3 days (range 15–703 days) in the PR group, and 170.8 ± 136.0 days (range 61–400 days) in the NR group (Table 11). The CR group showed a significantly longer survival time than the PR (p=0.029) and NR (p=0.027) groups, but there was no significant difference between the PR and NR groups (Figure 2).

3.5. Factors affecting survival time in CR patients

The CR group had a longer MST than other groups. However, there was variation in survival time within this group. Patients under 10 years of age had longer survival times than did patients over 10 years of age (under 10 years, 891.3 ± 416.4 days; over 10 years, 410.5 ± 229.1 days; p=0.011) (Figure 3 A). In addition, the presence of CVHD negatively affected the survival time of patients (non-CVHD group, 815.8 ± 413.6 days; CVHD group, 319.7 ± 180.6 days; p=0.002) (Figure 3 B). Reasons for hospitalization of patients who were categorized in CR are shown in Table 12. Interestingly, patients without a history of hospitalizing side effect (HSE) had a longer survival time than patients did who were hospitalized (non-hospitalization, 835.0 ± 455.8 days; hospitalization, 408.6 ± 233.0 days; p=0.031) (Figure 3 C).

4. Discussion

Various studies had analyzed the prevalence of lymphoma in dogs, differences in prognosis according to treatment methods, and factors affecting prognosis (Baskin et al., 2000, Jagielski et al., 2002, Gavazza et al., 2009, Marconato et al., 2011). In this study, WBC count of stage 5 patients were significantly higher than that of stage 3 and stage 4. Because lymphoma was a kind of hematological neoplasia, bone marrow metastasis occurred easily, as the disease progresses. It caused lymphocytosis, which resulted in leukocytosis in CBC analysis. One previous study investigated that peripheral blood smear to confirm lymphocytosis and presence of lymphoblast was worthy identifying stage 5 of lymphoma patients without bone marrow biopsy (Martini et al., 2015). Therefore, when evaluating the stage of a patient, if leukocytosis was visible in the CBC even if bone marrow biopsy was not performed, the possibility of stage 5 should be taken into account, referring to whether or not lymphocytosis was present.

There was no correlation between survival time and stage and substage in this study. This finding indicated that disease progression and the presence of clinical signs at the time of diagnosis were not critical factors for predicting prognosis. One previous study found that stage 4 was a positive prognostic factor (Baskin et al., 2000), however, in most studies, higher stages of lymphoma or substage b were negative factors (Jagielski et al., 2002, Ponce et al., 2004, Sorenmo et al., 2010, Garrett et al., 2002). Additional studies to evaluate the relationship between prognosis and stage or substage in small breed dogs are needed. Additionally, in

many previous studies, immunophenotype was revealed as an important prognostic factor and B cell type was positive prognostic factor. However, in this study, there was no relationship between immunophenotype and MST. Because number of patients could affect this result, evaluation through more cases can be beneficial.

In this study, the percentages of CR and PR patients were 54.3% and 31.4%, respectively, with a total response rate of 85.7%. In previous studies that evaluated the therapeutic response to CHOP, response rates varied from 81.3% to 100% (Gavazza et al., 2009, Childress et al., 2018, Burton et al., 2013, Curran and Thamm, 2016). These results highlight that even small breed dogs show a good response to treatment of multicentric lymphoma with the CHOP protocol like doing in large breed dogs. CR patients showed a significantly longer survival time than did PR or NR patients. Previous studies targeting large breed dogs, showed that the degree of response to treatment could act as a factor affecting the survival time, too (Jagielski et al., 2002).

We also evaluated factors that influence survival time due to variances within CR. Patients under 10 years of age showed longer survival times than those over 10 years. There were fewer precursor cells in the bone marrow of older animals than in young animals, which rendered older patients more vulnerable to myelosuppression caused by chemotherapy (Pinto et al., 2003). Another study found that older dogs responded better to the CHOP protocol, with PR rather than CR (Childress et al., 2018). As the response to treatment is an important prognostic factor, it tends to decrease with age, which in turn means that the MST may decrease according to age.

Patients with CVHD had shorter survival times than those that did not. Notably, CVHD was more prevalent in small breeds than in large breeds (Atkins et al., 2009).

Doxorubicin, one of the components of the CHOP protocol, had acute cardiotoxicity (Hallman et al., 2019) and a rise in troponin was reported in patients with lymphoma (Selting et al., 2004). Additionally, there were reports that a high dose of cyclophosphamide could result in cardiotoxicity in humans (Zver et al., 2007). Under the influence of these medications during chemotherapy, patients with CVHD probably had a shorter survival time than those without CVHD. There were studies for decreasing a risk of chemotherapy drugs and cardioprotective agents such as dexrazoxane and carvedilol were subjects of these studies. In human and canine, several studies suggested that the use of cardioprotective agents with anthracycline drugs, such as doxorubicin, was beneficial to decrease myocardial damage (Asselin et al., 2016, Kheiri et al., 2018, FitzPatrick et al., 2010), but others suggested that these agents could reduce the anti-cancer effect of cytotoxic drugs (Vejpongsa et al., 2014). Because the efficacy of using cardioprotective agents with chemotherapy was controversial, more prospective studies designed for evaluating the efficacy are needed.

We observed that hospitalizing side effect (HSE) of chemotherapy was a negative prognostic factor. Side effects such as gastrointestinal (GI) toxicity, pancreatitis, myelosuppression, and sepsis were mainly present in multidrug chemotherapy with CHOP protocol (Price et al., 1991, Vaughan et al., 2007, Wang et al., 2015). Some studies had shown that dose reduction due to myelosuppression after chemotherapy was associated with prolonged survival (Wang et al., 2015, Sorenmo et al., 2010). However, side effects could make it difficult to proceed with chemotherapy and reducing the dose or delaying the injection schedule might affect remission (Sorenmo et al., 2010). These HSE could lead to differences in survival

time and were considered to be negative prognostic factors. In this study, the cause of HSE was various. There was an effort to reduce side effect of chemotherapy in human. One of studies was focused on the preventive effect of curcumin and according to this study, curcumin could be beneficial for many kinds of side effect such as myelosuppression, GI toxicity, and so on (Liu et al., 2018). Since there were studies in dogs that applied curcumin as an anti-oxidant (Campigotto et al., 2020, Glodde et al., 2018), more studies are needed to evaluate its application as an ingredient to prevent side effects of chemotherapy.

This study was conducted by relying on medical records and there were some limitations because not all medical records were perfect. One of them were missing of information for assessing patients. A crucial example was results of FNA of liver or spleen. It made these patients be classified lower stage. Another consideration was patients who still alive at the end date of study. We defined a survival time of these patients was the duration from diagnosis to end date of this study. It may devaluate the survival time, too. This devaluated information can distort the statistical analysis. In addition, some of the result of this study differed from other previous studies. One study reported differences in prevalence according to sex. According to that study, intact female had lower risk than other sex (Villamil et al., 2009). Another study reported an influence of immunophenotype to prognosis. In this study, there was no correlation between prevalence and sex and immunophenotype did not affect the survival time. It is thought that further studies of a larger number of cases were needed to compare these differences with previous studies.

Despite these limitations, no previous study has evaluated lymphoma in small breed dogs. In this study, we analyzed the prevalence and prognostic factors of

canine multicentric lymphoma in small breed dogs treated with CHOP protocol. Response to CHOP treatment acted as an important prognostic factor. Furthermore, age, presence of CVHD, and HSE from chemotherapy were important prognostic factors within the CR group. These results will be beneficial for confirming the clinical characteristics and outcome information reported in small breed dog lymphoma patients and to help elucidate the best treatment and prognosis for these dogs.

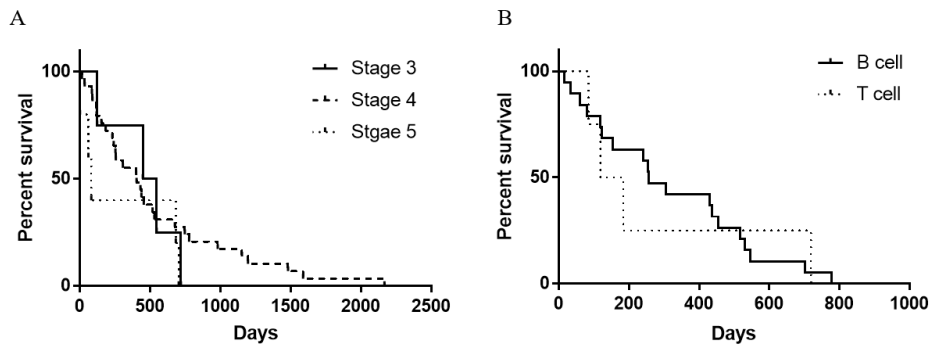

Figure 1. Distribution of survival time according to stage and substage and immunophenotype at diagnosis. A, the mean survival time (MST) was 459.3 (± 250.6), 552.7 (± 527.5) and 305.8 (± 354.8) days in stage 3 (n=21), stage 4 (n= 12), and stage 5 (n=5), respectively; B, MST was 317.9 (± 230.4) days in B cell type and 276.8 (± 297.7) days in T cell type. According to these results, stage including substage and immunophenotype did not affect survival time.

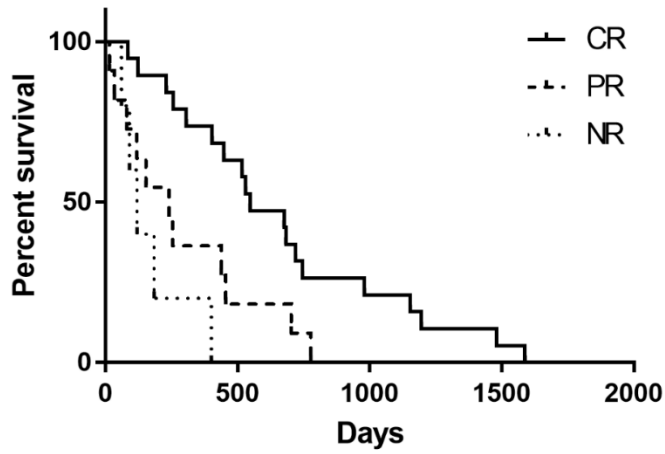

Figure 2. Variation of survival time in each response group. Mean survival time (MST) and the range were as follows; 666.9 ± 436.7 days and 85 to 1,588 days in CR (n=19); 297.2 ± 263.3 days and 15 to 703 days in PR (n=11); 170.8 ± 136.0 days and 61 to 400 days in NR (n=5). MST of CR is statistically significantly longer than PR or NR (p=0.029, p=0.027, respectively).

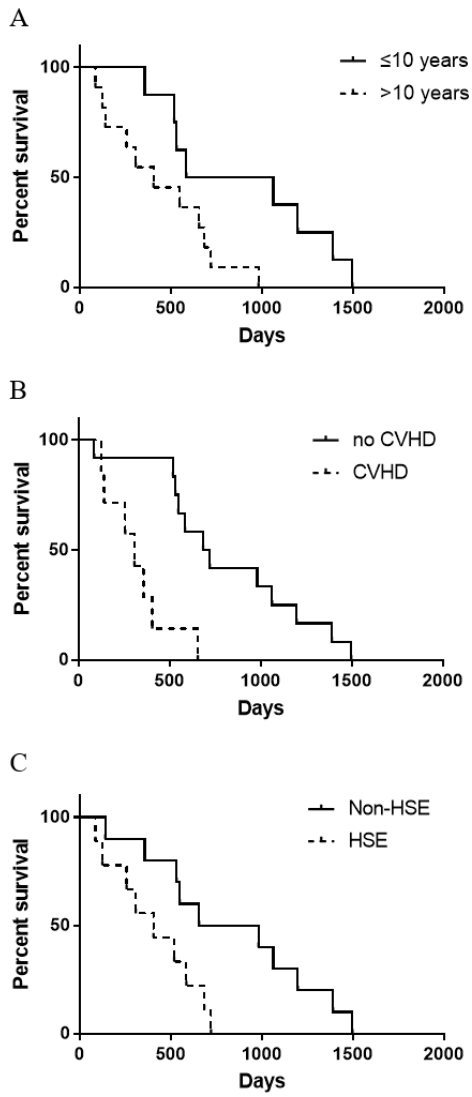

Figure 3. Distribution of different survival time according to influencing factors. Age (A), presence of cardiovascular heart disease (CVHD, B) and hospitalizing side effect (HSE, C) made a difference in the survival time. A, patients under 10 years (n=8) had longer survival time than those who over 10 years (n=11, p=0.011); B, patients who did not have CVHD (n=12) had longer survival time than those who had CVHD (n=7, p=0.002); C, patients who did not have HSE (n=9) had longer survival time than those who have HSE (n=10, p=0.031).

Table 1. CHOP treatment protocol for canine multicentric lymphoma

Weeks	1	2	3	4	6	7	8	9	11	13	15	17	19	21	23	25
Vincristine 0.7 mg/m^2 intravenous	○		○		○		○		○		○		○		○	
Cyclophosphamide 250 mg/m^2 intravenous or per oral		○				○				○				○		
Doxorubicin 1 mg/kg intravenous				○				○				○				○
Prednisolone (mg/m^2)	40	30	20	10												

Table 2. Information of 38 patients who were included in this study

Patient number	Age	Body weight (kg)	Sex[1)]	Breed	Stage	Substage	Diagnostic method	Immuno-phenotype	Survival time (days)	Overall response	Presence of CVHD[2)]	Presence of HSE[3)]
1	2	5.02	IM	Dachshund	3	a	FNA, FACS	B	676	CR	X	O
2	3	13.73	NM	Welsh corgis	4	a	FNA, PARR	B	438	PR	X	O
3	6	3.80	IF	Yorkshire Terrier	3	a	FNA, PARR	B	1,588	CR	X	X
4	6	10.80	NM	Cocker spaniel	3	a	FNA	-	2,168	-	X	X
5	6	4.23	NM	Maltese	4	b	FNA, PARR	B	517	CR	X	O
6	7	4.40	NF	Maltese	4	a	FNA, PARR	B	1,154	CR	X	X
7	7	5.50	NF	Shih-tzu	3	a	FNA, FACS	B	400	SD	X	X
8	7	3.40	NM	Maltese	3	b	FACS	B	530	CR	X	X
9	8	8.61	IF	Poodle	3	a	FNA, PARR	B	118	PR	X	X
10	8	5.86	IM	Coton de Tulear	4	a	FNA, PARR	B	153	PR	X	O
11	9	7.64	NF	Shih-tzu	4	b	FNA	-	1,196	CR	X	X
12	9	7.40	NF	Shih-tzu	4	b	FNA, PARR	B	15	PR	X	X
13	9	15.00	NF	French Bulldog	3	a	FNA, FACS	B	254	PR	X	O

[1)] IM: intact male, NM: neutered male, IF: intact female, NF: neutered female.

[2)] Cardiovascular heart disease.

[3)] Hospitalizing side effect.

Table 2. Information of 38 patients who were included in this study (continued)

Patient number	Age	Body weight (kg)	Sex	Breed	Stage	Substage	Diagnostic method	Immuno-phenotype	Survival time (days)	Overall response	Presence of CVHD	Presence of HSE
14	9	4.90	NF	Poodle	3	a	FNA, FACS	B	448	CR	O	X
15	9	8.00	NM	Schnauzers	3	a	FNA, PARR	B	1,481	CR	X	X
16	9	6.00	NM	Shih-tzu	5	a	FNA, PARR	B	703	PR	O	X
17	10	9.40	NF	Cocker spaniel	5	a	FNA, PARR	B	61	PD	O	X
18	10	4.55	NF	Shih-tzu	4	b	FNA, PARR	T	184	SD	X	O
19	10	4.08	NM	Mongrel	5	b	FNA, PARR	-	683	CR	X	O
20	10	3.00	NM	Yorkshire Terrier	3	a	-	B	547	CR	X	X
21	10	4.89	NM	Shih-tzu	3	b	FNA	B	306	CR	O	O
22	11	3.15	NF	Pomeranian	3	a	FNA, FACS	B	256	CR	O	O
23	11	11.00	NM	Pug	4	b	FNA, PARR	-	981	CR	X	X
24	11	3.20	NM	Miniature Pinscher	4	b	FNA, PARR	-	90	SD	X	O
25	12	6.67	NF	Shih-tzu	5	b	FNA, PARR	-	1	-	X	X
26	12	11.40	NF	Cocker spaniel	3	a	FNA, FACS	B	746	CR	O	X
27	12	10.28	NF	Shih-tzu	4	a	FNA, PARR	B	241	PR	X	O
28	12	6.62	NF	Shih-tzu	3	a	FNA, PARR	B	777	PR	X	X

Table 2. Information of 38 patients who were included in this study (continued)

Patient number	Age	Body weight (kg)	Sex	Breed	Stage	Substage	Diagnostic method	Immuno-phenotype	Survival time (days)	Overall response	Presence of CVHD	Presence of HSE
29	12	3.85	NF	Maltese	3	a	FNA, PARR	B	455	PR	X	X
30	12	3.73	NF	Maltese	3	a	FNA, PARR	T	85	CR	X	O
31	12	8.00	IM	Spitz	3	a	FNA, PARR	T	119	SD	O	O
32	13	2.34	NF	Maltese	4	a	FNA, PARR	B	431	-	X	X
33	13	8.93	IF	Cocker spaniel	3	b	FNA	B	34	PR	X	O
34	13	3.30	IF	Maltese	3	a	FNA, FACS	B	231	CR	O	X
35	13	7.15	NM	Mixed	5	b	FNA, FACS	B	81	PR	X	O
36	14	4.68	NF	Shih-tzu	3	a	FNA, PARR	B	123	CR	O	O
37	15	4.18	NF	Miniature Pinscher	3	a	FNA, PARR	T	719	CR	X	O
38	15	5.10	NM	Shih-tzu	4	a	FNA	-	404	CR	O	O

Table 3. Signalments of patients who were included in this study

Signalments	Value
Age (years) (mean ± S.D., range)	9.8 ± 3.0, 2~15
Body weight (age) (mean ± S.D., range)	6.3 ± 3.1, 2.3~15.0
Sex	
Intact female (n, %)	4, 10.5
Neutered female (n, %)	18, 47.4
Intact male (n, %)	3, 7.9
Neutered male (n, %)	13, 34.2

The mean age of all patients was 9.8 years and mean body weight was 6.3 kg. The number of female patients was more numerous than that of male patients.

Table 4. Comparison of mean survival time according to sex

Sex	Neutered	Mean survival time Mean ± S.D. (days)
Female	X	492.8 ± 734.6
	O	419.2 ± 366.0
Male	X	316.0 ± 312.2
	O	686.8 ± 577.0

Sex was divided into four categories, reflecting whether patients were neutered or not. There were no significant differences about mean survival time according to sex.

Table 5. Breeds distribution of patients in this study

Breeds	Number of dogs (%)
Shih-tzu	11 (28.9)
Maltese	7 (18.4)
Cocker spaniel	4 (10.5)
Poodle	2 (5.3)
Yorkshire terrier	2 (5.3)
Miniature pinscher	2 (5.3)
Mongrel	2 (5.3)
Coton de tulear	1 (2.6)
Dachshund	1 (2.6)
French bulldog	1 (2.6)
Pomeranian	1 (2.6)
Pug	1 (2.6)
Schnauzers	1 (2.6)
Spitz	1 (2.6)
Welsh corgis	1 (2.6)
Total	38 (100)

Table 6. Stage and substage distribution of patients with multicentric lymphoma

Variables		Number of patients (%)
Stage[1)]	Substage[2)]	
1	a	No patients
	b	No patients
2	a	No patients
	b	No patients
3	a	18 (47.4)
	b	3 (7.9)
4	a	6 (15.8)
	b	6 (15.8)
5	a	2 (5.3)
	b	3 (7.9)

[1)] Stage 1, single lymph node involvement; stage 2, regional involvement of multiple lymph node; stage 3, generalized lymph node involvement; stage 4, involvement of liver and/or spleen with stage 1-3; stage 5, involvement of bone marrow with stage 1-4.

[2)] Substage a, absence of clinical signs; b, presence of clinical signs.

Table 7. Complete blood count analysis of patients with multicentric lymphoma

Variables	Mean ± S.D.
White blood cell[1)] (/μl)	15,257.8 ± 9,295.5
Stage 3	13,548.6 ± 8,460.6
Stage 4	12,678.2 ± 6,514.0
Stage 5	28,112.0 ± 8,572.8
Packed cell volume[2)] (%)	38.6 ± 7.6
Stage 3	39.9 ± 6.3
Stage 4	37.3 ± 7.9
Stage 5	35.8 ± 12.3
Platelet[3)] ($\times 10^4$/μl)	28.6 ± 16.7
Stage 3	31.3 ± 17.1
Stage 4	25.5 ± 17.4
Stage 5	24.7 ± 14.8

[1)] Reference range: 5,200-17,000/μl.
[2)] Reference range: 37.1-57.0%.
[3)] Reference range: 14.3-40.0$\times 10^4$/μl.

Table 8. Blood analysis classification of patient population

Variables		Low	Normal	High	Total
Complete Blood Count	WBC	1	23	13	37
	PCV	17	20	-	37
	PLT	6	23	7	36
Serum Chemistry	ALT	-	21	9	30
	ALP	-	12	18	30
	BUN	3	19	3	25
	Creatinine	-	25	-	25
	Total bilirubin	-	25	5	30
	Total protein	11	15	2	28
	Albumin	4	25	1	30
Electrolyte	Sodium	12	19	2	33
	Potassium	-	33	-	33

-: no patients who were included in this classification.

Table 9. Serum chemistry and electrolyte analysis of patients

Variables (Unit) (Reference range)	Stage	Mean	S.D.
ALT[1] (U/L) (5.8-83.3)	3	60.2	26.2
	4	113.0	109.1
	5	111.3	92.6
ALP[2] (U/L) (0-97.9)	3	201.9	209.3
	4	1,064.0	1,342.7
	5	924.0	1,262.6
BUN[3] (mg/dL) (9.6-31.4)	3	18.8	7.8
	4	15.6	7.1
	5	30.6	14.0
Creatinine (mg/dL) (0.4-1.3)	3	0.7	0.2
	4	0.8	0.2
	5	0.8	0.1
Total bilirubin (mg/dL) (0-0.2)	3	0.1	0.1
	4	0.2	0.5
	5	0.8	1.5
Total protein (g/dL) (5.7-7.5)	3	6.4	1.2
	4	5.9	1.2
	5	5.4	1.4
Albumin (g/dL) (2.6-4.4)	3	3.6	0.7
	4	3.3	0.7
	5	2.9	0.6
Sodium (mmol/L) (145.1-152.6)	3	146.2	5.9
	4	145.8	2.0
	5	146.1	2.7
Potassium (mmol/L) (3.6-5.5)	3	4.4	0.4
	4	4.5	0.4
	5	4.9	0.2

[1] Alanine aminotransferase.
[2] Alkaline phosphatase.
[3] Blood urea nitrogen.

Table 10. Patients population and mean survival time according to the immunophenotype

Immunophenotype	Number of patients (%)	Mean survival time Mean ± S.D. (days)
B cell type	27 (71.1)	317.9 ± 230.4
T cell type	4 (10.5)	276.8 ± 297.7
Not assessed patients	7 (18.4)	Not assessed
Total	38 (100)	310.7 ± 236.2

Immunophenotypes were determined by FACS or PARR and 7 patients were not assessed about their immunophenotype. Mean survival time (MST) of total patients was evaluated with the exception of 7 patients whose immunophenotype were not assessed. There were no statistical differences in MST according to immunophenotype.

Table 11. Number of patients and survival time according to response

Response	Number of patients (%)	Mean survival time (days) Mean ± S.D. (range)
Complete remission (CR)	19 (54.3)	666.9 ± 436.7 (85-1,588)
Partial remission (PR)	11 (31.4)	297.2 ± 263.3 (15–703)
No remission (NR) [stable disease (SD) and progressive disease (PD)]	5 (14.3)	170.8 ± 136.0 (61–400)

Total response rate, which was sum of CR and PR, was 85.7% in this study. Mean survival time was the longest in CR patients (666.9 days) significantly compared to PR (297.2 days) and NR (170.8 days) patients.

Table 12. Reasons for hospitalization of patients who were categorized in complete remission

Patients number[1)]	Hospitalizing side effect
1	Extravasation
5	Pancreatitis
19	Bacterial enteritis, azotemia, respiratory failure
21	Hyperthermia after treatment
22	Neutropenia
30	Gastrointestinal irritation
36	Cardiopulmonary edema
37	Extravasation
38	Extravasation

[1)] Patient number is same as Table 2.

Hospitalizing side effects were various from hyperthermia to extravasation. Extravasation was the most common reason of hospitalization.

5. REFERENCES

VAIL, D. M., THAMM, D. H., LIPTAK, J. M. 2019. Hematopoietic tumors. *Withrow and MacEwen's Small Animal Clinical Oncology***,** 688.

ZANDVLIET, M. 2016. Canine lymphoma: a review. *Veterinary Quarterly,* 36**,** 76-104.

MORTIER, F., DAMINET, S., VANDENABEELE, S., VAN DE MAELE, I. 2012. Canine lymphoma: a retrospective study (2009-2010). *Vlaams Diergeneeskundig Tijdschrift,* 81**,** 341-351.

CHUN, R. 2009. Lymphoma: which chemotherapy protocol and why? *Topics in Companion Animal Medicine,* 24**,** 157-162.

SORENMO, K., OVERLEY, B., KRICK, E., FERRARA, T., LABLANC, A., SHOFER, F. 2010. Outcome and toxicity associated with a dose-intensified, maintenance-free CHOP-based chemotherapy protocol in canine lymphoma: 130 cases. *Veterinary and Comparative Oncology,* 8**,** 196-208.

KIUPEL, M., TESKE, E., BOSTOCK, D. 1999. Prognostic factors for treated canine malignant lymphoma. *Veterinary Pathology,* 36**,** 292-300.

CHILDRESS, M., RAMOS-VARA, J., RUPLE, A. 2018. Retrospective analysis of factors affecting clinical outcome following CHOP-based chemotherapy in dogs with primary nodal diffuse large B-cell lymphoma. *Veterinary and Comparative Oncology,* 16**,** E159-E168.

JAGIELSKI, D., LECHOWSKI, R., HOFFMANN-JAGIELSKA, M., WINIARCZYK, S. 2002. A retrospective study of the incidence and

prognostic factors of multicentric lymphoma in dogs (1998–2000). *Journal of Veterinary Medicine Series A,* 49**,** 419-424.

MILLER, A., MORLEY, P., RAO, S., AVERY, A., LANA, S., OLVER, C. 2009. Anemia is associated with decreased survival time in dogs with lymphoma. *Journal of Veterinary Internal Medicine,* 23**,** 116-122.

BASKIN, C. R., COUTO, C. G., WITTUM, T. E. 2000. Factors influencing first remission and survival in 145 dogs with lymphoma: a retrospective study. *Journal of the American Animal Hospital Association,* 36**,** 404-409.

KIRKWOOD, J. K. 1985. The influence of size on the biology of the dog. *Journal of Small Animal Practice,* 26**,** 97-110.

OLSON, R. D., MUSHLIN, P. S. 1990. Doxorubicin cardiotoxicity: analysis of prevailing hypotheses. *The Journal of the Federation of American Societies for Experimental Biology,* 4**,** 3076-3086.

FELDMAN, E. 2004. Canine hyperadrenocorticism. *Canine and Feline Endocrinology and Reproduction***,** 252-357.

CHERRONE K.L., DEWEY C.W., COATES J.R., BERGMAN R.L. 2004. A retrospective comparison of cervical intervertebral disk disease in nonchondrodystrophic large dogs versus small dogs. *Journal of the American Animal Hospital Association*, 40, 316-320

CRABTREE, A. C., SPANGLER, E., BEARD, D., SMITH, A. 2010. Diagnostic accuracy of gray-scale ultrasonography for the detection of hepatic and splenic lymphoma in dogs. *Veterinary Radiology & Ultrasound,* 51**,** 661-664.

MARTINI, V., MELZI, E., COMAZZI, S., GELAIN, M. 2015. Peripheral blood

abnormalities and bone marrow infiltration in canine large B-cell lymphoma: is there a link? *Veterinary and Comparative Oncology,* 13**,** 117-123.

GAVAZZA, A., SACCHINI, F., LUBAS, G., GUGLIUCCI, B., VALORI, E. 2009. Clinical, laboratory, diagnostic and prognostic aspects of canine lymphoma: a retrospective study. *Comparative Clinical Pathology,* 18**,** 291.

MARCONATO, L., STEFANELLO, D., VALENTI, P., BONFANTI, U., COMAZZI, S., ROCCABIANCA, P., CANIATTI, M., ROMANELLI, G., MASSARI, F., ZINI, E. 2011. Predictors of long-term survival in dogs with high-grade multicentric lymphoma. *Journal of the American Veterinary Medical Association,* 238**,** 480-485.

PONCE, F., MAGNOL, J.-P., LEDIEU, D., MARCHAL, T., TURINELLI, V., CHALVET-MONFRAY, K., FOURNEL-FLEURY, C. 2004. Prognostic significance of morphological subtypes in canine malignant lymphomas during chemotherapy. *The Veterinary Journal,* 167**,** 158-166.

GARRETT, L. D., THAMM, D. H., CHUN, R., DUDLEY, R.. VAIL, D. M. 2002. Evaluation of a 6-month chemotherapy protocol with no maintenance therapy for dogs with lymphoma. *Journal of Veterinary Internal Medicine,* 16**,** 704-709.

BURTON, J. H., GARRETT-MAYER, E., THAMM, D. 2013. Evaluation of a 15-week CHOP protocol for the treatment of canine multicentric lymphoma. *Veterinary and Comparative Oncology,* 11**,** 306-315.

CURRAN, K., THAMM, D. 2016. Retrospective analysis for treatment of naive canine multicentric lymphoma with a 15-week, maintenance-free CHOP protocol. *Veterinary and Comparative Oncology,* 14**,** 147-155.

PINTO, A., DE FILIPPI, R., FRIGERI, F., CORAZZELLI, G., NORMANNO, N. 2003. Aging and the hemopoietic system. *Critical Reviews in Oncology/hematology,* 48**,** S3-S12.

ATKINS, C., BONAGURA, J., ETTINGER, S., FOX, P., GORDON, S., HAGGSTROM, J., HAMLIN, R., KEENE, B., LUIS-FUENTES, V., STEPIEN, R. 2009. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *Journal of Veterinary Internal Medicine,* 23**,** 1142-1150.

HALLMAN, B. E., HAUCK, M. L., WILLIAMS, L. E., HESS, P. R., SUTER, S. E. 2019. Incidence and risk factors associated with development of clinical cardiotoxicity in dogs receiving doxorubicin. *Journal of Veterinary Internal Medicine,* 33**,** 783-791.

SELTING, K., LANA, S., OGILVIE, G., OLMSTEAD, A., MYKLES, D., BRIGHT, J., RICHARDSON, K., WALTON, J., MONNET, E., FETTMAN, M. 2004. Cardiac troponin I in canine patients with lymphoma and osteosarcoma receiving doxorubicin: comparison with clinical heart disease in a retrospective analysis. *Veterinary and Comparative Oncology,* 2**,** 142-156.

ZVER, S., ZADNIK, V., BUNC, M., ROGEL, P., CERNELC, P., KOZELJ, M. 2007. Cardiac toxicity of high-dose cyclophosphamide in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. *International Journal of Hematology,* 85**,** 408-414.

ASSELIN, B. L., DEVIDAS, M., CHEN, L., FRANCO, V. I., PULLEN, J., BOROWITZ, M. J., HUTCHISON, R. E., RAVINDRANATH, Y., ARMENIAN, S. H., CAMITTA, B. M. 2016. Cardioprotection and safety

of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma: a report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. *Journal of Clinical Oncology,* 34**,** 854.

KHEIRI, B., ABDALLA, A., OSMAN, M., HAYKAL, T., CHAHINE, A., AHMED, S., OSMAN, K., HASSAN, M., BACHUWA, G., BHATT, D. L. 2018. Meta-analysis of carvedilol for the prevention of anthracycline-induced cardiotoxicity. *The American Journal of Cardiology,* 122**,** 1959-1964.

FITZPATRICK, W., DERVISIS, N. G., KITCHELL, B. 2010. Safety of concurrent administration of dexrazoxane and doxorubicin in the canine cancer patient. *Veterinary and Comparative Oncology,* 8**,** 273-282.

VEJPONGSA, P., YEH, E. T. 2014. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. *Journal of the American College of Cardiology,* 64**,** 938-945.

PRICE, G. S., PAGE, R. L., FISCHER, B. M., LEVINE, J. F., GERIG, T. M. 1991. Efficacy and toxicity of doxorubicin/cyclophosphamide maintenance therapy in dogs with multicentric lymphosarcoma. *Journal of Veterinary Internal Medicine,* 5**,** 259-262.

VAUGHAN, A., JOHNSON, J. L., WILLIAMS, L. E. 2007. Impact of chemotherapeutic dose intensity and hematologic toxicity on first remission duration in dogs with lymphoma treated with a chemoradiotherapy protocol. *Journal of Veterinary Internal Medicine,* 21**,** 1332-1339.

WANG, S., LEE, J., LIAO, A. 2015. Chemotherapy-induced neutropenia is

associated with prolonged remission duration and survival time in canine lymphoma. *The Veterinary Journal,* 205**,** 69-73.

LIU, Z., HUANG, P., LAW, S., TIAN, H., LEUNG, W., XU, C. 2018. Preventive effect of curcumin against chemotherapy-induced side-effects. *Frontiers in Pharmacology,* 9, 1374.

CAMPIGOTTO, G., ALBA, D. F., SULZBACH, M. M., DOS SANTOS, D. S., SOUZA, C. F., BALDISSERA, M. D., GUNDEL, S., OURIQUE, A. F., ZIMMER, F., PETROLLI, T. G. 2020. Dog food production using curcumin as antioxidant: effects of intake on animal growth, health and feed conservation. *Archives of Animal Nutrition,* 74**,** 397-413.

GLODDE, F., GUNAL, M., KINSEL, M. E., ABUGHAZALEH, A. 2018. Effects of natural antioxidants on the stability of omega-3 fatty acids in dog food. *Journal of Veterinary Research,* 62**,** 103-108.

VILLAMIL, J. A., HENRY, C. J., HAHN, A. W., BRYAN, J. N., TYLER, J. W., CALDWELL, C. W. 2009. Hormonal and sex impact on the epidemiology of canine lymphoma. *Journal of Cancer Epidemiology,* 2009.

국 문 초 록

소형견에서 CHOP로 치료를 받은 다중심성 림프종 환자에 대한 후향적 연구

지도교수 윤 화 영

서울대학교 대학원
수의학과 임상수의학(수의내과학) 전공
김 태 희

림프종은 개에서 가장 흔한 악성 종양 중 하나이다. Vincristine, cyclophosphamide, doxorubicin, prednisolone을 조합해 사용하는 항암치료(CHOP 프로토콜)는 다중심성 림프종에서 가장 효과적인 치료법이다. 이전의 여러 연구들에서 CHOP 프로토콜에 대한 치료 반응 및 예후 인자들에 대해 평가를 해왔지만, 소형견에 초점을 맞춘 연구들은 부족하다.

이 연구에서는 다중심성 림프종을 가진 15 kg 이하의 소형견에서 CHOP 프로토콜을 이용해 치료를 했을 때의 치료 결과와 예후 인자에 대해 조사하였다. 2014년부터 2020년 9월까지 다중심성 림프종을 진단받고, CHOP 프로토콜을 이용하여 치료를 받은 15 kg 이하의 소형견들이 이 연구에 포함되었다. 이 환자들을 대상으로 CHOP 치료에 대한 반응을 평가하였다.

전체 38마리의 환자들 중에서 54.3%가 완전 완화(complete remission, CR)를 보였으며, 31.4% 환자에서 부분 완화(partial remission, PR)를 보였고, 나머지 14.3% 환자에서는 완화를 보이지 않았다(no remission, NR). 완전 완화를 보인 환자들과 부분 완화를 보인 환자들을 합한 비율인 전체 완화율(response rate)은 85.7%였다. 연구 대상이 된 모든 환자의 평균 생존기간은 490.6 ± 474.5일이었다. CR, PR, NR 그룹의 평균 생존기간은 각각 666.9 ± 436.7일, 297.2 ± 263.3일, 170.8 ± 136.0일이었으며, 평균 생존기간이 PR그룹(*p*-value 0.029)과 NR그룹(*p*-value 0.027)과 비교하여 CR을 나타낸 그룹에서 통계적으로 유의적으로 길었다. CR을 보인 환자들 중에서 나이가 10살 이하인 환자들의 평균 생존기간(891.3 ± 436.7일)이 10살 초과인 환자들의 평균 생존기간(410.5 ± 229.1일)보다 길었다(*p*-value 0.011). 또한 기저질환 중 심장질환이 없는 환자들의 평균 생존기간(815.8 ± 413.6일)이 심장질환이 있는 환자들의 평균 생존기간(319.7 ± 180.6일)보다 길었다(*p*-value 0.002). 마지막으로 항암치료 후 발생한 부작용으로 입원한 이력이 없는 환자들의 평균 생존기간(944.6 ± 396.3일)이 입원한 이력이 있는 환

자들의 평균 생존기간(369.8 ± 201.8일)보다 길었다(*p*-value 0.031).

이 연구에서는 기존의 연구들과 다르게 15kg 이하의 소형견에 초점을 맞춰 다중심성 림프종 환자에서 CHOP 치료에 대한 반응을 조사하였다. 그 결과 완화율이나 생존기간의 측면에서는 이전 연구에서 확인된 치료 반응과 유사한 결과를 보였으며, 소형견에서도 CHOP 치료에 대한 반응이 중요한 예후 인자로 작용하고, CR을 보인 환자들 중에서도 나이, 심장질환의 유무, 항암 치료로 인하여 입원할 정도의 부작용 이력이 중요한 예후 인자이다. 특히 소형견에서 잘 발생하는 심장질환의 유무가 림프종의 치료에 있어 중요한 예후 인자로 작용할 수 있다는 점을 확인했다는 것이 이 연구의 큰 의의 중 하나이다.

이러한 결과들은 치료 결과에 대한 정보를 확인하고 환자의 상태에 맞는 최선의 치료 방법을 안내하고, 치료에 따른 예후를 설명하는데 도움이 될 것이다.

주요어: 림프종, 소형견, 생존기간, 예후 인자

학 번: 2019–21265