Original Article

Initial response to L-asparaginase and prednisolone induction chemotherapy in 107 cases of canine lymphoma

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Abstract

In 107 dogs with canine lymphoma, induction chemotherapy was performed with L-asparaginase (10,000 IU/m²) and prednisolone (median dose, 40 mg/m²), and the initial responses were analyzed. The initial remission rate was high, at 92.3% (CR: 27.9% and PR: 64.4%), in 104 assessed cases. In terms of anatomical sites, the remission rate for multicentric lymphoma was significantly higher than that for cutaneous lymphoma ($p=0.045$). No significant differences were observed in remission rates by stage, substage, or prior corticosteroid administration. No severe side effects, such as anaphylaxis or clinically evident pancreatitis, were seen. The results suggested that L-asparaginase induction chemotherapy was an effective early induction agent for downstaging canine lymphoma.

Key word : Canine, L-asparaginase, Lymphoma, Remission rate, Side effects

Introduction

Canine lymphoma accounts for 7–24% of all canine tumors and 83% of all canine malignant hematopoietic tumors [21]. Lymphoma is highly sensitive to chemotherapy, and many studies on the treatment of lymphoma have been published [2, 4, 6, 7, 9, 13–15, 18, 22, 25]. The CHOP protocol is the foundation for multidrug regimens, and it has been reported that co-administration of L-asparaginase with CHOP therapy further improves response rates and lengthens the first remission period [19, 21].

However, in 2005 it was reported that adding L-asparaginase to the CHOP protocol did not improve remission or survival periods [8, 10]. Therefore, it may be more appropriate to reserve the use of L-asparaginase for treating relapse in dogs with lymphoma that have failed induction therapy [10].

The toxicity of chemotherapy is well known, and in the ACOPA II protocol the mortality during induction with doxorubicin and prednisone was 22% within 22 days [15]. Stage/substage was not shown in these cases. The mortality during induction with the high-dose Madison-Wisconsin protocol was 27% because of chemotherapy toxicity [5]. The trend toward including a greater number of substage b dogs possibly resulted in more treatment-related deaths in the high-dose group compared to the controls. The investigators reported that only stage was identified as being predictive for death due to toxicity. In particular, the higher the stage of lymphoma, the greater the incidence of severe side effects was. However, the toxicity of L-asparaginase has been reported to be low [11, 16], and it is considered a safe induction agent that can prevent deaths due to side effects. The objectives of this study were to describe the initial response and side effects to L-asparaginase and prednisolone induction chemotherapy in canine lymphoma.

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Materials and Methods

Client-owned dogs presented to the Oncology Department of Azabu University Veterinary Teaching Hospital from April 1992 to October 2008 and diagnosed with lymphoma by either diagnostic cytology or histopathology were analyzed retrospectively ($n=107$). They had not received chemotherapy but may have received prednisolone alone prior to the study. Dogs were assessed within 1 week, and dogs with lymphoblastic leukemia were not included in this study.

For initial induction, L-asparaginase and prednisolone were administered, and their initial effects were assessed. The data were assessed at the first visit within 1 week after L-asparaginase induction. Efficacy was assessed based on medical records and the remission rate. Response Evaluation Criteria In Solid Tumors (RECIST) were used to assess the response to treatment [20]. Complete remission (CR) was defined as disappearance of all target lesions, and partial remission (PR) as a size reduction of $\geq 30\%$ in the sum of the longest diameters of the lesions. Remission rates were calculated by adding CR and PR. Stable disease (SD) was defined as a reduction of $<30\%$ or an increase of $<20\%$ in the sum of the longest diameters of the lesions, and progressive disease (PD) was defined as an increase of $\geq 20\%$ in the sum of the longest diameters of the lesions (the appearance of one or more new lesions was also considered progression).

Except for 2 of the 107 dogs, the dosage of L-asparaginase was $10,000 \text{ IU/m}^2$. For the two dogs, the dosage of L-asparaginase was $8,000 \text{ IU/m}^2$, and $5,000 \text{ IU/m}^2$, respectively. The median dosage of prednisolone was 40 mg/m^2 (range, $10\text{--}40 \text{ mg/m}^2$).

The recorded data included breed, sex, age, body weight, anatomical site, WHO stage and substage, prior corticosteroid administration, L-asparaginase and prednisolone dosages, initial remission following L-asparaginase induction, improvements in clinical symptoms, and clinical and hematological abnormalities recorded at the first visit after L-asparaginase induction. Improvements in clinical symptoms were assessed by a medical record review of activity, appetite, body weight fluctuation, respiratory symptoms, diarrhea, and ocular lesions. Body weight fluctuations were classified into three categories: "Unchanged" was defined for variations within $\pm <5\%$, "increased" was defined as an increase of $\geq 5\%$, and "decreased" was defined as a decrease of $\geq 5\%$. Clinical and hematological abnormalities seen at the first visit after L-asparaginase induction were classified using the veterinary co-operative oncology group common terminology criteria for side effects (VGOG-CTCAE) [23].

The Mann-Whitney U test was used to compare remission rates in relation to anatomical sites (multicentric and cutaneous), stages, substages, and prior corticosteroid administration. The level of significance was set at $p < 0.05$.

Results

Twenty-six breeds were represented in this study. The most common breed was Golden Retriever ($n=32$, 29.9%), followed by Shetland Sheepdog ($n=9$, 8.4%), Shih Tzu ($n=8$, 7.5%), Pembroke Welsh Corgi ($n=5$, 4.7%). There were 52 males (15 castrated) and 55 females (31 spayed), with a median age of 7 years (range, 1–16 years) and a median body weight of 14.5 kg (range, 2.2–67.9 kg). The anatomical sites were classified as follows ($n=107$): Multicentric ($n=89$, 83.2%), cutaneous ($n=14$, 13.1%), mediastinal ($n=1$, 0.9%), digestive tract ($n=1$, 0.9%), and duplicate (digestive tract and mediastinal, digestive and multicentric, each $n=1$, 1.9%). Only the multicentric cases ($n=89$) were subjected to stage classification: II ($n=3$, 3.4%), III ($n=5$, 5.6%), IV ($n=12$, 13.5%), and V ($n=69$, 77.5%) (Table 1). The classification of substages in the multicentric cases was as follows: Substage-a ($n=33$, 37.1%) and substage-b ($n=56$, 62.9%). Prednisolone was given prior to L-asparaginase induction chemotherapy in 38 dogs (35.5%) and was not administered in 69 dogs (64.5%).

After administration of L-asparaginase and prednisolone, 104 cases were assessed. There were 29 CR cases (27.9%), 67 PR cases (64.4%), 6 SD cases (5.8%), and 2 PD cases (1.9%). Three dogs with multicentric lymphoma (2.8%) died within 1 week (Table 2). The overall remission rate (CR plus PR) was 92.3%.

In terms of anatomical sites, the initial remission rate was 96.5% for multicentric lymphoma (CR: 26 cases and PR: 57 cases) in 86 cases, and 78.6% for cutaneous lymphoma (CR: 2 cases and PR: 9 cases) in 14 cases; the remission rate was significantly higher for multicentric lymphoma than for cutaneous lymphoma ($p=0.045$). The initial remission rate for

Table 1. Initial stage of multicentric lymphoma.

Stage	Number of cases
I	0 (0%)
II	3 (3.4%)
III	5 (5.6%)
IV	12 (13.5%)
V	69 (77.5%)

Table 2. Response rate and stage classification of all, multicentric lymphoma (3 cases died within 1 week of induction.), cutaneous and other types.

Response	All	Multicentric All stages	Stage II	Stage III	Stage IV	Stage V	Cutaneous	Others
CR	29 (27.9%)	26 (30.2%)	0 (0.0%)	2 (40.0%)	1 (8.3%)	23 (34.8%)	2 (14.3%)	1 (25.0%)
PR	67 (64.4%)	57 (66.3%)	3 (100.0%)	2 (40.0%)	11 (91.7%)	41 (62.1%)	9 (64.3%)	1 (25.0%)
SD	6 (5.8%)	3 (3.4%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	2 (3.0%)	3 (21.4%)	0
PD	2 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)

CR : Complete response, PR : Partial response, SD : Stable disease, PD : Progressive disease.

Table 3. Frequency and grade of clinical and hematological abnormalities after L-asparaginase administration.

	Grade I	Grade II	Grade III	Unknown
Increased ALP	10	5	6	—
Increased ALT	5	1	10	—
Anemia	8	1	3	—
Increased plasma bilirubin	1	0	1	—
Creatinine	0	0	1	—
Thrombocytopenia	1	0	1	—
Neutropenia	2	0	0	—
Diarrhea	8	2	2	1
Vomiting	2	1	0	—
Fever	0	1	0	—

multicentric lymphoma was 100% for Stage II (PR:100%), 80% for Stage III (CR:40% and PR:40%), 100% for Stage IV (CR : 8.3% and PR : 91.7%), and 97.0% for Stage V (CR : 34.8% and PR : 62.1%) ; there were no significant differences between the stages. The initial remission rate for substage-a was 93.9% (CR : 10 cases (30.3%), PR : 21 cases (63.6%) and SD : 2 cases (6.1%)), while for substage-b it was 92.9% (CR : 16 cases (28.6%), PR : 36 cases (64.3%), SD 1 case (1.8%) and death 3 cases (5.4%)) ; there were no significant differences between the substages. The initial remission rate was 92.1% (35 cases) and 88.4% (61 cases) with and without prednisolone administration prior to L-asparaginase induction chemotherapy, respectively ; there was no significant difference between the two rates.

With regard to improvements in clinical symptoms, improvements were seen in 31 of the 35 dogs (88.6%) with lethargy, and increased appetite was seen in 33 of the 39 dogs (84.6%) with anorexia. Body weight fluctuations were assessed in 96 dogs : body weight increased in six dogs (increased by $\geq 5\%$), decreased in 33 dogs (decreased by $\geq 5\%$), and remained unchanged in 57 dogs. Symptoms improved in eight of the 17 dogs with respiratory symptoms, in eight of the 19 dogs with ocular lesions, and in three of the 12 dogs with diarrhea.

In all 104 cases, common clinical and hematological abnormalities seen during the first week were increased : ALP 21 cases (20.2%), ALT 16 cases (18.3%), anemia 12 cases (11.5%), and diarrhea 13 cases (12.5%) (Table 3). In this study, severe side effects, such as anaphylaxis or clinically evident pancreatitis, were not seen.

Discussion

The initial remission rate for L-asparaginase induction chemotherapy was 92.3% (CR : 27.9% and PR : 64.4%), and,

in particular, the initial remission rate for multicentric lymphoma was high at 96.5% (CR:30.2% and PR:66.3%), which resembles that reported in past studies on multidrug regimens such as COP 89% [6], ACOPA II 75% [15], COPLA/LVP 92% [2], and UW25 89% [7]. The remission rate for L-asparaginase and prednisolone combination therapy was higher than that for prednisone alone (48%) [1, 3]. In the present study, prednisolone was coadministered, but the favorable results obtained were possibly due to the effects of L-asparaginase.

With regard to the general condition of the dogs, improvements were seen in 88.6% of the dogs with lethargy and in 84.6% of dogs with anorexia, and QOL improved in a number of dogs. Although appetite increased in many of the dogs, the body weight decreased by $\geq 5\%$ in 33 dogs (34.4%).

As to effects at different anatomical sites, the remission rate was significantly higher for multicentric lymphoma than for cutaneous lymphoma ($p=0.045$). No significant differences were seen in remission rates among the various stages and substages, thus suggesting the efficacy of L-asparaginase in all stages.

A previous study reported significant differences in survival with long-term corticosteroid administration [17]. In this study, administration periods and doses varied from those in that study, but no significant difference existed in the initial remission rate between dogs with and without prior corticosteroid administration. Therefore, corticosteroid administration prior to chemotherapy does not appear to affect the initial response, but it should be avoided from the viewpoint of lymphoma diagnosis and induction of multidrug resistance.

Many clinical and hematological abnormalities were seen within the first week of L-asparaginase and prednisolone administration, but most abnormalities were low grade as assessed by VCOG-CTCAE, and no therapy was required in most dogs. The increased activities of hepatic enzymes (ALP and ALT) were probably caused by the effects of corticosteroids. Diarrhea and vomiting were mostly mild, and pancreatitis was not suspected. In general, bone marrow suppression is not a common side effect of L-asparaginase. The grade III anemia seen in three dogs may not be related to the bone marrow toxicity because it was not associated with severe neutropenia. The typical side effects of L-asparaginase include anaphylaxis, DIC, and pancreatitis [12, 24], but in this study, no such severe side effects were observed. However, it will be necessary to analyze side effects associated with repeated L-asparaginase administration. In this study, three dogs died after L-asparaginase induction; all three dogs had stage Vb lymphoma. One dog died of pulmonary edema, and two dogs may have died of lymphoma progression, L-asparaginase-related side effects or tumor lysis syndrome, but the actual causes of their deaths were unclear.

In recent years, studies have documented that the use of L-asparaginase in multidrug regimens had no effect on remission and survival periods, negating the therapeutic effects of L-asparaginase administered as induction chemotherapy for lymphoma [8, 10]. This led to a re-examination of the use of L-asparaginase. However, in this study, a high initial remission rate was obtained, and no severe side effects were seen. In this report, we assessed the initial response rate but not survival time, but the results suggested that the combination of L-asparaginase and prednisolone was an effective early induction agent for downstaging canine lymphoma. It was reported that dogs receiving high-dose chemotherapy survived longer than those on a conventional protocol, but the trend toward using a greater number of substage b dogs possibly resulted in more treatment-related deaths in the high-dose group compared to the controls [5]. Therefore, it may be possible to use of L-asparaginase and prednisolone safely to downstage dogs with lymphoma, and the downstaging may have a role in achieving further safe induction chemotherapy.

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犬リンパ腫107例における L-アスパラギナーゼと プレドニゾロンの初期導入による反応の検討

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■ 和文要約

犬のリンパ腫107例に対して、L-アスパラギナーゼとプレドニゾロンにより初期導入を行い、その反応を分析した。評価可能であった104例のうち、寛解率は92.3%（完全寛解27.9%、部分寛解64.4%）であった。皮膚型リンパ腫より多中心型リンパ腫の方が、有意に寛解率が高かったものの（ $p=0.045$ ）、ステージ、サブステージ、ステロイド投与歴による差は認められなかった。臨床的に有意なアナフィラキシー反応や膵炎は認められなかった。以上のことから、L-アスパラギナーゼとプレドニゾロンによるダウンステージを目的とした導入は、有効であると考えられた。

Key word : Canine, L-asparaginase, Lymphoma, Remission rate, Side effects

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