A Preliminary Report
Chemotherapy Versus Chemotherapy Plus Immunotherapy in the Treatment of lymphosarcoma in the Dog

Köpeklerde Lenforsakoma’nın Kemoterapi ve Kemoterapi + immünoterapi ile sağ損害ının karşılaştırılması

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SUMMARY

Fifteen dogs with malignant lymphoma were presented at the Faculty of Veterinary Medicine of the University of Istanbul. 7 of the 15 dogs were not treated. Remaining 8 dogs were divided into two group. The first group consisted of 4 dogs and was treated with cyclic combination chemotherapy (L-asparaginase, vincristine, cyclophosphamide, methotrexate, prednisolone, adriamycin and leukenan). 4 dogs of the second group were treated with the same combination chemotherapy protocol plus immunotherapy with alpha interferon.

The mean survival time of the 7 untreated dogs was 70.7 days which compared with mean survival time of 225 days for the chemotherapy group. 4 dogs subjected to chemotherapy plus immunotherapy had a mean survival time of 591.3 days.

Key words: Dog, Lymphosarcoma, Chemotherapy, Immunotherapy.

INTRODUCTION

Malignant lymphoma occurs relatively frequently in the dog and, if untreated, is an aggressive, rapidly fatal disease. Malignant lymphoma or lymphosarcoma is the most common hematopoietic neoplasm of dogs, accounting for 5 to 7 per cent of all canine tumors seen. Despite defective endogenous retroviral elements in a cell line of canine lymphosarcoma and in the canine genome were isolated. Viral aetiology have not yet been proven. There is no known sex predilection. All breeds may be affected but the boxer, basset hound, Saint Bernard, Scottish terrier, and many hunting breeds appear to have greater risk (1,3,4,7,10,14,15,18).

Lymphosarcoma can develop in any organ, but there are four major clinically recognised forms, based on the gross distribution of the disease (1,7,10,15,18) In order of decreasing occurrence, they are:

1. Generalized (multicentric) 84 %
2. Alimentary 6.9 %
3. Thymic (anterior mediastinal) 2.2 %
4. Extranodal 6.9 %

Clinical staging is an attempt to define the true extent of a tumor at a given time. The accepted criteria currently used for staging canine lymphoma were established by the World Health Organization. There is no significant correlate than the apparent clinical extent of the disease (1,10,18).

Clinical signs may be related to the anatomic form of the disease but are usually nonspecific. Generalized lymphadenopathy, weight loss, anorexia, abdominal distention, hepatomegaly, splenomegaly, dyspnea, and polyuria are common clinical features. For accurate diagnosis cytologic or histologic examinations should be performed (1,3,4,7,10,15,18).

Goals of canine lymphosarcoma treatment are life prolongation and improved quality of life. A specific objective in the treatment of canine lymphosarcoma is induction of clinical remission. Another objective is to manage secondary complications of the disease, such as pseudohyperparathyroidism, tumor lysis syndrome (1,6,10,18).

Several drugs have been used either singly or in combination to treat the neoplasm with variable success (2,5,8,9,10,11,12,15,18), Generally combination che-
motherapy is preferred since, if the cytotoxic cocktail is properly formulated, 1) the fraction of cells destroyed by each drug is different for each substance, 2) the toxic effects are borne by different organs, 3) the actions is carried out during various phases of the growth cycle of the cell and 4) the is a delay in the start of of the cell's resistance to chemotherapy (1,7,10).

Experimental evidence indicates that dogs with lymphosarcoma have an immune deficiency in the cellular (T-cell) component of the immune system. The findings are the basis for the use of immunotherapy as a treatment for canine lymphosarcoma. Although chemotherapy with autologous vaccines of tumor cells have produced the best results, Immunotherapy alone has not been effective in treatment of canine lymphosarcoma (10,18).

Interferons are a group of substances that has received quite extensive study in human oncology, and to a very limited degree in veterinary oncology. Interferons can be directly cytotoxic or have secondary immunostimulatory effect. The critical mechanism operative at the cellular level is unclear, but they may be mediated by the same inhibitors of DNA and RNA synthesis that occur in virus-infected cells. Relatively low doses of interferons have been shown to enhance antibody formation and lymphocyte blastogenesis, while higher doses inhibit both these functions and have delayed hypersensitivity while enhancing macrophage phagocytosis and cytotoxicity. Lymphocyte cytotoxicity NK cell activity, and surface antigen expression (11,13,16,17).

The antitumor activity of alpha-interferon has been demonstrated in human patients with hematologic, breast, renal, and head and neck cancers, but the best responses have been seen in a variety of lymphomas. Bovine alpha-interferon has been used to treat feline leukemia.

Interferons tend to be species-specific; however, are underway with alphainterferon, which has been shown to have cross-species specificity, (11,13,16)

**MATERIALS AND METHODS**

Dogs-A total of 15 privately owned dogs were referred to the Faculty of Veterinary Medicine of the University of Istanbul by practicing veterinarians for confirmation of diagnosis and treatment of lymphosarcoma. Owners of 7 dogs did not consent to treatment after histologic diagnosis. These dogs were evaluated as the control group. The rest of the dogs were divided into two groups: (a) combination chemotherapy group (4 dogs) and (b) combination chemotherapy plus alpha interferon therapy group (4 dogs). All treated dogs were maintained as outpatients. The animals were followed for sign of adverse reactions.

**Clinical Study**

**Patient Selection**

All animals were subjected to physical examination (fig. 1), history evaluation and histological interpretation of biopsy sample. After histological diagnosis, 7 of 15 dogs were not treated because the owners did not consent to this.

Extant of the disease were determined on the basis of results of hematological ant biochemical testing, thoracic and abdominal radiographs (fig. 2), lymph node biopsy, and bone marrow aspiration. The characteristics of 15 dogs are given in (Table 1).

Dogs were staged according to a modified World Health Organization (WHO) staging system (Table 2).
Table 3. School of Veterinary Medicine, University of Wisconsin-Madison, Canine Lymphoma Protocol

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>DATE</th>
<th>DOSE GIVEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Vincristine 0.5-0.7 mg/m² IV</td>
<td>400 IU/kg L-Asparaginase 1M</td>
</tr>
<tr>
<td>Week 1</td>
<td>2mg/kg Prednisone PO daily</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Cyclophosphamide 200-250 mg/m² IV or PO</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Vincristine 0.5-0.7 mg/m² IV</td>
<td>1 mg/kg Prednisone PO daily</td>
</tr>
<tr>
<td>Week 4</td>
<td>Doxorubicin 30 mg/m² IV</td>
<td>0.5 mg/kg Prednisone PO daily</td>
</tr>
<tr>
<td>MAINTENANCE</td>
<td>Vincristine 0.5-0.7 mg/m² IV</td>
<td>0.25 mg/kg Prednisone PO daily</td>
</tr>
<tr>
<td>Week 7</td>
<td>Chlorambucil 1.4 mg/kg PO</td>
<td>(if in complete remission)</td>
</tr>
<tr>
<td></td>
<td>Stop prednisone</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>Vincristine 0.5-0.7 mg/m² IV</td>
<td></td>
</tr>
<tr>
<td>Week 9</td>
<td>Methotrexate 0.5-0.8 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Week 10</td>
<td>Vincristine 0.5-0.7 mg/m² IV</td>
<td></td>
</tr>
<tr>
<td>Week 11</td>
<td>Chlorambucil 1.4 mg/kg PO</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>Vincristine 0.5-0.7 mg/m² IV</td>
<td></td>
</tr>
<tr>
<td>Week 13</td>
<td>Doxorubicin 30 mg/m² IV</td>
<td>(1) Continue as above (week 8-13) treatments every 2 weeks, alternating methotrexate and doxorubicin. After week 28, treatments can be given every 3 weeks.</td>
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<tr>
<td>(2) Maximum dose of doxorubicin 175-225 mg/m². Then stop doxorubicin and continue methotrexate.</td>
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<td>(3) Monitor weekly CBC for first 12 weeks, then periodically thereafter. Stop chemotherapy if WBC 3,000 and administer prophylactic antibiotics.</td>
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Fig. 3. Mesenteric lymph nodes were enlarged and lymphatics are full.

Fig. 4. Mediastinal and pulmonary involvement.

Fig. 5. Splenic involvement.

Fig. 6. Used skin test for evaluation of cell mediated immunity.

mended supportive therapies in the literature were applied. Also when the platelet count dropped below 50,000, or the total WBC dropped below 3,000 cells/mm³ of blood, the protocol was delayed until there was evidence of rising cell counts.

Square meters of body surface area was preferred for drug dosage calculations. Thus severe toxicosis was not seen.

Evaluation

Treatment results and survival times were evaluated in each group. Complete response (CR) was defined as absence of all known disease; partial response (PR) was evaluated as at least 50% tumor reduction without the appearance of new lesions; no response (NR) was defined as a less than 50% tumor regression. 2 of 15 dogs were referred for necropsy after death and histological interpretations were made to determine the toxic effects of drugs and the final situations of the tumor involvement (fig. 3,4,5). A skin test (Multitest CMI, Institute Mérieux, Lyon, France) was used to evaluate cell-mediated immunity (fig. 6).

In addition to the chemotherapy protocol above, alpha interferon (Intron A Injection, 3 million IU vials, Schering Corporation, Nej Jersey-USA) were administered 3 million IU/m daily between 4-6 weeks of the chemotheraphy in chemotheraphy plus immunotherapy group.

RESULTS

Lymphosarcoma encountered dog breeds were crossbred (6), German Shepherd dog (5), Boxer (1), York
Shire Terrier (1), Whippet (1) respectively. It was interesting that all dogs, except 1 crossbred female dog, were classified as stage 1, 2 as stage II, 6 as stage III, 3 as stage IV.

Initially, 12 dogs presented high levels of alkaline phosphatase and LDH. 5 dogs had hypercalcemia and 6 dogs had high levels of SGPT, and in 1 dog postcaval syndrome was present. Alpha fetoprotein levels were in the normal ranges. But during the treatment there was an increasing decrease in the levels. Other parameters tested (SGOT, creatinine, blood urea, total protein, glucose) were not changed either by chemotherapy or immunotherapy. Leucocyte counts were slightly decreased by chemotherapy and increased significantly by interferon therapy.

During therapy physical examinations did not detect any abnormalities and appetites remained unchanged. Behavioral alterations were not observed. Acute systemic anaphylaxis reactions were not seen by interferon therapy.

The skin test which used to evaluate cell-mediated immunity was revealed an increase of cell mediated immunity as parallel to the increase in the leucocyte count.

After 48 hours of chemotherapy administration the enlarged lymph nodes returned to their normal size.

Only one dog with postcaval syndrome presented severe depression and anorexia after sudden tumor lysis but regular fluid and medical treatment prevented more a serious scene. The table was evaluated as a result of the tumor lysis syndrome.

When relapses were observed in advanced cases many dogs were euthanized upon the owners' request.

**DISCUSSION**

Because different articles suggest different dog breed as being under greater risk for canine lymphosarcoma. (1,3,10,18), It is difficult to put forward the presence of genetic predisposition. However, small dog breeds have been shown to be at low risk.

No sex predilection is evident, although intact females appear to be at lesser risk. It was interesting that 15 of the 16 cases in our study were male. Also females have better prognosis than males (1,7,10,18).

Mean 5.05 years of age in our study was parallel to the literature data.

Lymphosarcoma is a rapidly fatal disease and without treatment dogs have an average survival time of less than a few weeks after diagnosis. In our study, untreated dogs survived for less than 2 months (1,10,18).

Goals of canine lymphosarcoma treatment are life prolongation and improved quality of life. Radiation therapy can be used to treat solitary or extranodal lymphomas as an adjunct to chemotherapy; however, its application is limited since most dogs have the multicentric form of the disease. Immunotherapy alone has not been effective in the treatment of canine lymphosarcoma (1,3,12,18). But newer work with biologic response modifiers is promising, and they will probably be evaluated soon in the treatment of canine lymphosarcoma. The goal of our study was to evaluate the effectiveness of immunotherapy with alpha interferon as an adjuvant of the best treatment modality-chemotherapy. 3x106 I.U. alpha interferon was administered daily by slow intra venous injection without any allergic reactions for 15 days in the interval of the Wisconsin University chemotherapy protocol.

Eventually, immunotherapy with alpha interferon plus chemotherapy was more effective than chemotherapy alone with the mean survival time 225 days to 593.1 days respectively.

We are in the opinion than our study which is a preliminary report will support similar studies on this subject.

**REFERENCES**


ARAŞTIRMALAR ÖZETİ

Atta Exertional Rhabdomyolysis (ER) Patofizyolojisi

Stephanie Valberg


Yazarın tecrübelere göre sağlamda etkileden solisyonların tayinına Acepromazin, Detomudin ve non-steroidal antiefamatuarları ön plana bulunmaktadır. Her ne kadar etki mekanizması açığa kavuştuşumakla birlikte özel lke Acepromazin'in direkt olumlu etkisi etkileyici bulunmaktadır.