Canine Lymphoma as a Potential Model for Experimental Therapeutics

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Summary. Spontaneous lymphoma is a frequently occurring disease in the canine species. These neoplasms are remarkably similar to their counterpart in humans with respect to histology, anatomic sites of involvement, and biologic behavior. In the present study, dogs with biopsy proven lymphoma were treated with total-body irradiation and objective remissions of disease were observed. A small group of patients with generalized lymphosarcoma have been treated concurrently with total body irradiation, and these preliminary clinical results are comparable to our experience with dogs. The increased exploitation of canine lymphoma as a model for experimental therapeutics is encouraged.

Introduction. Malignant lymphoma in the canine species (1, 3, 6), suspected of being virus-induced (2), closely resembles its human counterpart in several respects. Canine lymphoma has been noted to be histologically similar not only to human lymphosarcoma but also to Burkitt's lymphoma (5), and a comparable histopathologic classification has been proposed for animals (7). As with humans, dogs are most commonly afflicted during their middle and later years of life, and spontaneous cures have not been reported in the literature. The disease usually progresses fairly rapidly, leading to death within several months of diagnosis if the animals are not sacrificed.

The typical presenting sign in dogs is generalized lymphadenopathy which may be associated with weight loss, anemia, and fever. In addition to the obvious peripheral lymphadenopathy, autopsies have demonstrated diffuse mediastinal, retroperitoneal, and mesenteric lymph node involvement. Hepatosplenomegaly is a common finding in the advanced stages of disease and lymphomatous infiltration of other organ systems can also occur. Canine lymphoma thus constitutes a form of cancer in animals which is similar to its human type in several respects.

Experimental Methods and Results. Sixteen dogs with malignant lymphoma were referred by area veterinarians and admitted for study. A consistent clinical feature of the disease was generalized lymphadenopathy, most marked in the mandibular, scapular, inguinal, and popliteal regions. A number of animals were in the advanced stages of disease, four dying within three weeks from progressive lymphoma. The diagnosis of lymphosarcoma was established in each case from a lymph node biopsy. Several animals had a leukemoid (granulocytic) reaction as occasionally noted in humans with Hodgkin's disease, but the possibility of lymphocytic leukemia was ruled out by peripheral blood studies on each animal. The dogs were fed dry chow and water ad libitum and those with anorexia were offered canned meat products. The diarrhea which frequently developed during irradiation was treated with kapectate. None of the animals received blood transfusions or antineoplastic chemotherapy.

Total-body irradiation was administered with 2-million-volt X-rays from a Van de Graaff accelerator (SSD 340 cm, air dose rate 6.1 R per minute, H.V.L. 7.0 mm Pb). Table 1 summarizes the treatment regimens and responses, the exposures expressed being measured in air at the position of the midline of the animal. Daily treatments were on a five times per week basis with other fractionation schedules as indicated. The initial dose schedule (or sham) was randomly assigned, but the small number of animals and the marked variation in their clinical condition precluded any meaningful comparison of various fractionation schemes. Although conclusions cannot be drawn from this pilot study, the responders to treatment appeared to have an increased survival (median 13.0 weeks, mean 16.0 weeks) as compared to the nonresponders and sham (median 3.0 weeks, mean 5.4 weeks). The tendency for animals with better responses to have received a higher radiation dose was readily explained by improvement with treatment which appeared to result in longer survival and thus permitted continuation of treatment. Perpendicular measurements using the greatest diameters were made on lymph nodes prior to treatment and at weekly intervals thereafter. Responses in lymph node size in Table 1 represent changes in volume calculations using the formula for a sphere. Seven of the fourteen dogs treated with total-body irradiation had either complete or partial remission clinically, while the remaining animals had no uniform reduction of lymph node size or showed progression of disease during treatment.

The majority of the dogs experienced some bone marrow depression with total-body irradiation, as shown by moderate decreases in the white blood cell count, reticulocyte count, hemoglobin, and platelet count. Only one dog, which received a single exposure of 300 R, developed marked hematopoietic toxicity and died two weeks after irradiation, with diffuse bleeding secondary to thrombocytopenia. Except for this single dog, the remaining animals died from progressive lymphosarcoma and had extensive tumor involvement at autopsy. Aside from the slight to moderate bone marrow depression, the only evident toxicity from irradiation was diarrhea which occurred in most animals to some degree and was
Canine Lymphoma

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Total % node Survival</th>
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<tbody>
<tr>
<td>No.</td>
<td>Age (yr.)</td>
</tr>
<tr>
<td>1.</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>12</td>
</tr>
<tr>
<td>3.</td>
<td>9</td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
</tr>
<tr>
<td>5.</td>
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<td>6.</td>
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<td>7.</td>
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</tr>
<tr>
<td>16.</td>
<td>13</td>
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</tbody>
</table>

Total-body irradiation of canine lymphoma.

a Died from hemorrhage secondary to radiation induced bone marrow depression; all others died of progressive disease.

b Remission resulted from single exposure of 300 R.

controlled reasonably well with kapectate. A blinded (coded) review of the histopathology failed to reveal any apparent distinction between the responders and nonresponders in terms of tumor differentiation, mitotic index, or other obvious morphologic characteristics.

Clinical Methods and Results. Our experience with the total-body irradiation of humans with lymphosarcoma has been reported in part elsewhere (4) and will not be reviewed here in detail. To date, we have treated eighteen patients with generalized lymphosarcoma, thirteen of whom had lymphocytic (well-differentiated) lymphosarcoma. Canine lymphoma histologically corresponds more closely to lymphoblastic (poorly differentiated) lymphosarcoma; the five patients with this latter diagnosis are described in Table 2. The irradiation schedules for these five patients are quite similar to those employed for many of the dogs; two of these five patients have shown objective response to therapy. Patient #1 was maintained in remission for many months with no other treatment than intermittent doses of total-body irradiation. Patient #5 had induction of complete remission with total-body irradiation, following which additional radiation was locally delivered to the previously involved lymph nodes. Patient #2 demonstrated definite tumor regression in the cervical region during total-body irradiation while at the same time there was obvious progression of disease in the abdomen. This was analogous to the pattern of simultaneous regression and progression of disease in different sites as noted with each of several dogs.

Discussion. It is not intended to emphasize the possible similarity in radiation response between human and canine lymphoma. Any predictability of human radiosensitivity using canine lymphoma as a test system will be more adequately defined in the future when sufficient subjects have been studied to permit comparison. Rather we would stress the simulation of human lymphoma by these canine neoplasms with respect to histology, anatomic sites of involvement, and the behavior of the disease. The differential rates of tumor

Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total % node Survival</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Age (yr.)</td>
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<tr>
<td>2.</td>
<td>57</td>
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<tr>
<td>3.</td>
<td>42</td>
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<td>4.</td>
<td>32</td>
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<tr>
<td>5.</td>
<td>55</td>
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Total-body irradiation of human lymphoblastic lymphosarcoma.

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growth and response to treatment in various lymph nodes of
the same animal is an interesting correlation with clinical ex-
perience in humans. This contrasts with the more uniform
growth rate and response patterns of many experimentally
induced or transplanted tumor systems in rodents. Dogs are
likewise excellent subjects for the usual clinical procedures
such as biopsy (lymph node, organ, or bone marrow), serial
determination of chemistries, and diagnostic radiographic tests
(including lymphography). The authors encourage the in-
creased exploitation of canine lymphoma as a model for
experimental therapeutics.

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