Prolonged Disease-Free Survival in Dogs With Lymphoma After Total-Body Irradiation and Autologous Marrow Transplantation Consolidation of Combination-Chemotherapy-Induced Remissions

By Paul L. Weiden, Rainer Storb, H. Joachim Deeg, Theodore C. Graham, and E. Donnall Thomas

Dogs with spontaneous lymphoma were treated with one of three aggressive treatment protocols: (1) combination chemotherapy with cyclophosphamide, L-asparaginase, Oncovin®, and prednisone (CLOP); (2) combination chemotherapy with nitrogen mustard, Oncovin®, prednisone, L-asparaginase, and 6-mercaptopurine (MOPA-6); or (3) MOPA-6 followed by total-body irradiation (TBI) and autologous marrow transplantation. Of 14 dogs treated with CLOP, 9 achieved complete remission, but median disease-free survival was only 38 days. Of 57 evaluable dogs treated with MOPA-6, 34 (60%) achieved complete remission. Twelve dogs in complete remission received no additional therapy; median disease-free survival was 73.5 days, and the longest duration of complete remission was 113 days. Seventeen dogs in complete remission received 1100 R TBI followed by infusion of fresh marrow aspirated immediately prior to irradiation. Median disease-free survival was 206 days and was significantly prolonged compared to dogs receiving MOPA-6 alone (p < 0.01). Furthermore, 4 dogs remain alive in unmaintained complete remission 1–2 yr after irradiation. Thus, canine lymphoma was responsive to combination chemotherapy, but remissions were short. Consolidation of chemotherapy induced complete remission with TBI and autologous marrow transplantation prolonged disease-free survival and resulted in long-term unmaintained complete remission in a minority of dogs. This large animal model may help to define the role of TBI and autologous marrow grafting in the treatment of lymphoma.

MALIGNANT LYMPHOMA in the dog is a relatively common, aggressive, rapidly fatal disease. In general, the disease is initially responsive to various chemotherapy regimens or to total-body irradiation (TBI), but remissions are of brief duration and survival only minimally improved by therapy.

Autologous marrow transplantation has recently received renewed attention as an approach to delivering “supralethal” doses of chemotherapy and/or radiotherapy to patients with either hematologic or solid malignancies. Both conceptual and practical limitations of this approach are evident, however, emphasizing the need for studies in a relevant animal tumor model. We have previously explored the use of autologous marrow transplantation in conjunction with high-dose TBI or...
dimethyl myleran as initial therapy for dogs with lymphoma. Although these and other studies in dogs with lymphoma of aggressive chemotherapy or radiotherapy in conjunction with marrow transplantation were associated with excessive acute toxicity, it seemed likely that this toxicity could be reduced.

This article describes the development of an approach directed at long-term control of canine lymphoma using combination chemotherapy to induce complete clinical remissions, followed by consolidation of remissions using TBI and autologous marrow grafts. Three sequential series of dogs were studied. In the first, four active drugs (cyclophosphamide, L-asparaginase, vincristine, and prednisone) were used in combination; in the second, nitrogen mustard was substituted for cyclophosphamide and 6-mercaptopurine was added; and in the third, consolidation therapy with TBI and autologous marrow transplantation of dogs in chemotherapy-induced remissions was undertaken.

MATERIALS AND METHODS

Dogs Studied

Dogs with generalized adenopathy were referred by veterinarians with the consent of their owners as previously described. The diagnosis of malignant lymphoma was confirmed by examination of Wright-Giemsa-stained touch preparations and formalin-fixed, hematoxylin-eosin-stained sections of a peripheral lymph node biopsied under general anesthesia. Dogs admitted to our institution between July 1975 and February 1978 were eligible for inclusion in these studies. No dog was excluded because of advanced disease or poor overall clinical status, but 18 dogs died before beginning chemotherapy. Between July 1975 and March 1976, 14 dogs were initially treated with “CLOP” combination chemotherapy (see below). Between March 1976 and November 1976, 31 dogs were treated with “MOPA-6” (see below). No consolidation therapy was given to these dogs. Between December 1976 and February 1978, 36 dogs were started on MOPA-6 chemotherapy. Of these, 20 dogs (17 in complete remission and 3 in partial remission) were subsequently treated with TBI and autologous marrow grafts.

Assessment of Clinical and Tumor Status

All dogs received complete physical examinations, including measurement of submandibular, prescapular, popliteal, and inguinal lymph nodes, and complete blood counts before initiation of chemotherapy and at regular intervals thereafter. Overall clinical status was assessed by considering the general activity and appetite of the dog and the presence of infection, weight loss, or gastrointestinal symptoms and was subjectively graded as good, fair, or poor. Wright-Giemsa-stained bone marrow smears and Zenkers-fixed, hematoxylin-eosin-stained particle preparations were examined at the time of marrow aspiration for autologous marrow transplantation and as clinically indicated at other times. Blood chemistries were determined when clinically indicated, but were not routinely performed.

Complete remission was defined as the absence of palpably enlarged peripheral lymph nodes or abdominal organs. Dogs living less than 7 days were considered inevaluable. Partial remission was defined as greater than 50% reduction in the sum of perpendicular diameters of palpable nodes.

Chemotherapy

Chemotherapy was generally instituted 3–7 days after lymph node biopsy. In dogs with advanced disease, especially with edema of the head and neck, chemotherapy was begun on the day of biopsy. Dogs were given ampicillin and gentamicin from the day of lymph node biopsy until recovery of the peripheral granulocyte count after chemotherapy. Parenteral fluids, carbenicillin, and transfusions of red blood cells or platelets were administered as clinically indicated.

The initial chemotherapy regimen, CLOP, was modified from that described by Bull et al. Cyclophosphamide (C), 5 mg/kg, and vincristine (Oncovin®, O), 0.025 mg/kg, were administered on days 1 and 8; L-asparaginase (L), 250 μ/kg, and prednisolone (P), 2 mg/kg, were administered daily on days 1–14. All drugs were given intravenously. Day-8 administration of cyclophosphamide and vincristine was delayed if necessary until the peripheral leukocyte count was greater than 5000/μl.
The second chemotherapy regimen, MOPA-6, consisted of vincristine (Oncovin®, O), prednisolone (P), and L-asparaginase (A) as in CLOP. Nitrogen mustard (M), 0.2 mg/kg, was substituted for cyclophosphamide on days 1 and 8, and the antimetabolite, 6-mercaptopurine (6), 1 mg/kg, was given on days 1-14, unless the peripheral leukocyte count fell below 1500/μL.

Dogs that did not achieve complete remission after one course of therapy and dogs that relapsed were treated with second and subsequent courses of the protocol initially used to treat each dog.

**TB! and Autologous Marrow Transplantation**

Dogs on the third protocol were initially treated with one or two courses of MOPA-6 as above. Once in complete remission, they were returned home for 1-2 wk before readmission for irradiation and autologous marrow transplantation. During this interval, peripheral blood counts returned to normal, and weight gain was frequent. Dogs still in complete remission then received consolidation therapy.

Under general anesthesia, marrow was aspirated from both humeri and femurs and processed as previously described. Median number of nucleated marrow cells (corrected for peripheral blood cell contamination) was 1.3 x 10^9/kg body weight (range, 0.1-16.1 x 10^9/kg). A marrow sample for histologic examination was also obtained, but therapy was not influenced by the results of that examination, and no attempt was made to remove tumor cells. Immediately following marrow aspiration, the dog was irradiated by exposure to two opposing 60Co sources; 1100 R were delivered at 4.6 R/min—a lower dose rate than the 9.3 R/min used in previous studies from this laboratory in both normal dogs and dogs with tumors. The marrow, kept at 4°C for 4-5 hr, was infused i.v. upon completion of the irradiation. Postirradiation supportive care was as previously described, except that all dogs were treated with carbenicillin, 1 g/5 kg, b.i.d., beginning on day 3 following irradiation and marrow transplantation and continuing until the granulocyte count rose to more than 500/μL.

**Postprotocol Management and Follow-up**

Dogs were generally returned to their owners and referring veterinarians upon completion of the induction/consolidation therapy as outlined. Attempts were made to have each dog examined monthly by the referring veterinarian, but compliance by owners varied. Relapses were recorded whenever unequivocal recurrent adenopathy was observed. Most dogs were readmitted for additional courses of chemotherapy upon relapse, but owners' requests for euthanasia were granted. Since not all dogs were terminally ill when euthanized, survival times (while more accurate than remission durations or disease-free survivals) are shorter than if euthanasia were not permitted. Autopsy examinations were performed in 90% of dogs that died.

Remission duration and survival data were plotted by the method of Kaplan and Meier and compared using the log-rank procedure for failure data with censored observations.

**RESULTS**

**CLOP**

Fourteen dogs were treated with CLOP. All lived 7 or more days and 9 (64%) achieved complete remission. Five of these 9 died in their first remission 9-38 (median 17) days after starting therapy, generally with pneumonia in spite of normal peripheral granulocyte counts. Four dogs relapsed at 39-69 days, were retreated with CLOP, but died with tumor on days 133-265. Three dogs that achieved only partial responses and 2 dogs that did not respond to their initial courses of CLOP died 17-64 days after starting chemotherapy. Thus, even though 9 of 14 dogs achieved complete remission with CLOP, remission duration, relapse-free survival, and overall survival were short.

**MOPA-6**

Little acute toxicity was noted with MOPA-6 administration. The “day-8” administration of mustard and vincristine was delayed 1-4 days and/or nitrogen mustard was administered in reduced dosage because of persistent leukopenia in
one-half of the courses of MOPA-6. One moderate and one severe anaphylactic reactions to L-asparaginase were observed in 12 dogs given second courses of therapy.

Overall, 64 dogs were treated with the MOPA-6 chemotherapy regimen. Seven dogs survived less than 7 days after beginning therapy. Of the 57 dogs surviving 7 or more days, 34 (60%) achieved a complete remission and 23 did not. Eleven of the dogs that did not achieve complete remission died on days 7–21 of infection, 8 died on days 62–393 with tumor, 3 dogs were treated with TBI and autologous marrow (see below), and 1 dog is alive in unmaintained partial remission at greater than 2 yr.

Thirty-one dogs were treated prior to initiation of the TBI–autologous marrow consolidation protocol, and in these dogs, remission duration and survival data related to MOPA-6 chemotherapy alone can be obtained. Median duration of complete remission (obtained from Kaplan-Meier plot) was 83 days, and no dog remained in complete remission more than 113 days. Eight dogs that relapsed were retreated, and 6 achieved second complete remission lasting 18–104 (median 66) days. Only 2 dogs achieved a third complete remission and one of these achieved 5 complete remissions with MOPA-6. Median survival of all dogs that achieved complete remission with MOPA-6 was 223 days, and the longest survival was 393 days.

Eight of these 31 dogs were in “good” overall clinical condition when MOPA-6 was initiated. Six achieved complete remission, and median survival of all 8 dogs was 236 days. Of 12 dogs in fair condition, 3 achieved complete remission and median survival was 116 days, and of 11 dogs in poor condition, 3 achieved complete remission and median survival was only 8 days. Thus, overall clinical status at the time therapy was begun correlated both with likelihood of achieving complete remission and with median survival.

**MOPA-6–TBI**

Seventeen dogs alive in complete remission on days 26–105 after beginning chemotherapy were treated with TBI and autologous marrow. Of these, 13 had received 1 course and 4 had received 2 courses of MOPA-6 before irradiation. Bone marrow specimens obtained at the time of marrow aspiration were occasionally difficult to interpret, but contained no conclusive evidence of tumor in any dog.

Results are summarized in Table 1. One dog died on day 3 after TBI and marrow grafting of aspiration pneumonia. Sixteen dogs survived from 27 to more than 719

<table>
<thead>
<tr>
<th>Status at Time of TBI</th>
<th>No. of Dogs</th>
<th>Inadequate Marrow Recovery</th>
<th>Dead</th>
<th>Alive</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>With Tumor</td>
<td>Without Tumor</td>
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<tr>
<td>Complete remission</td>
<td>17</td>
<td>2</td>
<td>8</td>
<td>4*</td>
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<tr>
<td>Partial remission</td>
<td>3</td>
<td>1</td>
<td>3</td>
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*One died day 3; 1 killed day 27.
†Relapsed; now alive in remission after additional therapy.
(median 256) days after TBI, or 68 to more than 824 (median 318) days after starting chemotherapy. In general, the TBI and subsequent pancytopenia were tolerated with only moderate toxicity. One dog, however, developed severe inanition and partial posterior paresis, but ultimately recovered. Another dog developed generalized weakness, urinary incontinence, and deafness and was euthanized on day 27 after TBI at the owner’s request.

Hematopoietic recovery after TBI and autologous marrow infusion in these dogs is compared in Fig. 1 to the hematopoietic recovery observed in normal dogs treated in a similar manner. Two of the 17 dogs with lymphoma in remission failed to regain adequate marrow function after TBI and autologous marrow infusion. White blood cell counts remained <2200/µl and platelet counts remained <3000/µl (Fig. 1). Both dogs were euthanized (on days 50 and 104 after TBI) because of severe uncontrollable bleeding after they became refractory to random donor platelets. Marrow cell dose in one of these dogs was low (0.1 x 10^8 nucleated cells/kg body weight), but in the other was 1.4 x 10^8 cells/kg, i.e., above the median dose for all dogs. As shown in Fig. 1, an additional dog had delayed recovery of peripheral white blood cell counts, and 4 additional dogs had delayed recovery of peripheral platelet counts, but no clinical symptoms were attributed to delayed hematopoietic recovery in these dogs.

Nine dogs relapsed in peripheral nodes 46–308 (median 174) days after TBI or 106–337 (median 206) days after chemotherapy. Eight of these dogs have died and one remains alive after subsequent therapy. Four dogs are alive in unmaintained complete remission 377–719 days after TBI or 409–824 days after chemotherapy.

Fig. 1. Recovery of peripheral white blood cell and platelet counts after TBI and autologous marrow grafting. Range and median values observed in 13 normal dogs are indicated by shaded area and open squares, respectively. Values outside the normal range observed in 17 dogs with lymphoma in complete remission (solid circles and lines) and 3 dogs with lymphoma in partial remission (open circles and dashed lines) are indicated.
Remission duration from the first day of chemotherapy for the 17 dogs treated with TBI and autologous marrow is compared in Fig. 2 with that of a comparable group of dogs from the preceding MOPA-6 chemotherapy series, i.e., 8 dogs alive in complete remission 30 days after beginning chemotherapy that did not receive consolidation therapy. These curves are significantly different \((p < 0.0001)\), indicating that consolidation of drug-induced remissions with TBI and autologous marrow grafts resulted in a significant prolongation of remission duration.

Since therapy after relapse was not standardized, comparisons are difficult, but MOPA-6-treated dogs appeared to tolerate subsequent courses of chemotherapy better than did dogs treated with irradiation and autologous marrow. Owners of dogs treated with chemotherapy also accepted additional therapy for their dogs more readily than did owners of dogs treated with irradiation. As a result, survival after relapse in MOPA-6-treated dogs was longer than in TBI-treated dogs (93–296 [median 175] versus 13–131 [median 81] days). The survival curves of the two groups of dogs are depicted in Fig. 3. Median survival from the initiation of chemotherapy is not different for the two groups of dogs, but the only long-term disease-free survivors are from the group treated with irradiation and autologous marrow.

Three dogs in partial remission after two courses of MOPA-6 chemotherapy were treated with TBI and autologous marrow grafts (Table 1). Two dogs achieved

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*Fig. 2.* Kaplan-Meier plot of the probability of being in complete remission (expressed as percent) for the 8 dogs alive in complete remission 30 days after beginning chemotherapy (MOPA-6) and the 17 dogs in complete remission after MOPA-6 treated with TBI and autologous marrow transplantation (MOPA-6–TBI–BM). Day 0 is the day on which chemotherapy was initiated. Dogs alive in complete remission are indicated by open circles. The log-rank test was used to compare the results.

*Fig. 3.* Kaplan-Meier plot of the probability of survival for the dogs in Fig. 2. Dogs alive are indicated by open symbols.
complete remission but relapsed after 47 and 63 days, respectively, and survived 98 and 134 days after irradiation and marrow grafting. Both dogs showed some delay in hematopoietic recovery posttransplantation (Fig. 1). One dog showed no decrease in adenopathy and poor platelet recovery postgrafting (platelet count 700–4500/μl) (Fig. 1), became refractory to random donor platelets, and was euthanized because of diffuse bleeding 32 days after TBI and marrow grafting. This dog had received a low marrow cell dose (0.1 × 10^8 cells/kg). Thus, although complete remission could be achieved following TBI in two of three dogs in partial remission, hematopoietic recovery was delayed in all three dogs, and the two remissions were of only brief duration.

DISCUSSION

Induction of complete remission is the initial requirement for long-term control of malignant disease. Madewell and Squire et al. used cyclophosphamide, vincristine, and corticosteroids to treat dogs with lymphoma and achieved complete remission in 65% and 79% of dogs that lasted 80 (median) and 184 (mean) days, respectively. In an attempt to improve these results, Bull et al. added L-asparaginase to the chemotherapy regimen. L-asparaginase had been previously shown to be an extremely active agent against canine lymphoma and could be added in full dosage to the combination of cyclophosphamide, vincristine, and prednisolone. With this regimen, 30 of 52 dogs achieved complete remission, but 10 dogs died of complications of therapy. Two groups of investigators have utilized cytosine arabinoside in combination with cyclophosphamide, vincristine, and prednisone. Both achieved comparable results: 65%–75% complete remission and mean survival times of approximately 140 days. Since the data supplied in these reports of the results of combination chemotherapy of canine lymphoma are variable, and most importantly, since criteria for inclusion and therapy of individual dogs differ widely, comparisons of various regimens are difficult. Nevertheless, several conclusions can be drawn: (1) canine lymphoma is responsive to chemotherapy, i.e., the complete remission rate is high; but (2) remission duration is short (median approximately 40–80 days); (3) survival, while apparently prolonged compared to no or single drug therapy, is also relatively short; and (4) survival longer than 2 yr is rare.

In this study, we confirmed that administration of cyclophosphamide, L-asparaginase, vincristine, and prednisone to dogs with lymphoma was associated with unacceptable toxicity. Because cyclophosphamide is relatively poorly tolerated by dogs, nitrogen mustard, an alkylating agent of nearly comparable efficacy in treating lymphoma and relatively well tolerated by dogs, was substituted for cyclophosphamide in the five-drug MOPA-6 chemotherapy regimen. 6-Mercaptopurine, an antimetabolite, was added to decrease the likelihood of sensitizing dogs to L-asparaginase. Sixty percent of evaluable dogs treated with MOPA-6 achieved a complete remission. In the series of dogs treated with MOPA-6 alone, however, median remission duration and survival were still relatively short, and no dog remained alive in complete remission after 113 days.

Consolidation therapy of radiation or drug-induced complete remission is a well recognized tenet of modern medical oncology. One aggressive approach to consolidation therapy involves high-dose chemotherapy or radiotherapy in conjunc-
tion with autologous marrow transplantation to protect against otherwise lethal hematopoietic toxicity of the therapy regimen.\textsuperscript{11-15} An obvious theoretical objection to autologous marrow transplantation, particularly in malignancies involving the marrow, has been the likelihood that tumor cells aspirated with the marrow, and thus not exposed to the chemoradiotherapy administered to the patient, would result in the recurrence of the tumor after autologous marrow infusion.

Marrow involvement with lymphoma in dogs is common, e.g., was present on admission in 78% of 37 dogs in our initial study\textsuperscript{2} and at autopsy in 83% of 36 dogs examined by Van Pelt and Conner.\textsuperscript{3} Thus, even though the marrows of the dogs in complete remission at the time of TBI and autologous marrow grafting in the present study were apparently free of tumor at the time of marrow aspiration, it is possible, and perhaps likely, that some tumor cells were present in the marrow aspirates. Nevertheless, without any in vitro manipulation of the marrow to remove presumed tumor cells and without any postinfusion chemotherapy, long-term unmaintained complete remission has been observed in a substantial minority of dogs. The marrow of these individual dogs, of course, may have been free of tumor cells. Alternatively, the long-term disease-free survival of these dogs may be the result of altered growth potential of the tumor cells or of the environment of the host. Similar preliminary results in dogs with lymphoma have also been reported by Bowles.\textsuperscript{12} Furthermore, Appelbaum et al. have observed long-term disease-free survival of two patients with Burkitt's lymphoma given autologous marrow grafts, in spite of the detection of tumor in their marrow (although both patients were given chemotherapy between the time of detection of tumor in the marrow and marrow aspiration for cryopreservation).\textsuperscript{16} These results in dog and man suggest that marrow involvement, proven or likely, may not preclude long-term disease-free survival after autologous marrow infusion.

Previous attempts to utilize high-dose TBI in dogs with lymphoma have been limited by excessive toxicity, i.e., only 29 of 94 dogs with lymphoma (31%) survived more than 2 wk following 1200 R TBI.\textsuperscript{18,20,21} In the current study, however, 19 of 20 dogs receiving 1100 R survived more than 2 wk after TBI. This reduction in acute toxicity was most likely the result of several factors. First, the dose rate was reduced from 9.3 R/min to 4.6 R/min. Dose rate has previously been shown to affect toxicity in dogs.\textsuperscript{26,36} Second, all dogs receiving TBI in the current study had been permitted a "rest interval" between chemotherapy and irradiation and were in good clinical condition. In fact, most were in complete remission at the time of irradiation. Third, carbenicillin was added to the prophylactic antibiotic regimen administered during the postirradiation granulocytopenia.

However, these results highlight a potential problem of autologous grafting. In this study, the autologous marrow was neither cryopreserved nor manipulated in vitro to remove tumor cells. Nevertheless, marrow recovery was inadequate in 3 of 20 dogs, resulting in their deaths. In several other dogs, platelet recovery was prolonged compared with normal dogs undergoing autologous marrow transplants (Fig. 1). Some, but not all, of the dogs with delayed or inadequate hematopoietic recovery received relatively low numbers of nucleated marrow cells per kilogram body weight. It is not clear whether the observed impairment of hematopoietic recovery is related to stem cell damage resulting from the chemotherapy administered prior to marrow aspiration or to the lymphoma itself. Similar observations
were also made, however, in a previous study involving autologous marrow grafting in dogs with lymphoma that had not received chemotherapy prior to marrow aspiration. These results suggest that autologous marrow grafting, especially if the marrow is cryopreserved or manipulated in vitro with resultant cell loss, should be undertaken with caution in man.

The current study again demonstrates that randomly bred dogs with spontaneous lymphoma may be utilized for studies of potential relevance to man. The MOPA-6–TBI–autologous marrow graft protocol for the treatment of canine lymphoma described in this study resulted in prolongation of remission duration. More importantly, however, four dogs remain alive in unmaintained complete remission 1–2 yr after beginning chemotherapy. This observation at least raises the possibility that high-dose TBI consolidation in conjunction with autologous marrow grafting of combination-chemotherapy-induced remissions may result in long-term control of lymphoma.

In addition, these results pose an important question for future investigation: Are the relapses that occur the result of failure of the TBI to eradicate lymphoma cells present in the lymph nodes and organs of the dog, or the result of lymphoma cells present in the infused marrow? The common pattern of relapse after irradiation and autologous marrow grafting, i.e., recurrence of adenopathy without abnormalities of peripheral blood, suggests that the disease may not have been eradicated by the chemotherapy and TBI. To the extent that this is so, the results described in this report might be improved by more intensive chemoradiotherapy conditioning regimens. For example, it might be possible to increase the irradiation exposure, and thus the lymphoma cell kill, by use of fractionated TBI. Alternatively, if relapses are related to the presence of lymphoma cells in the marrow inoculum, results might be improved by in vitro treatment of the marrow to eliminate tumor cells. Possible approaches include physical methods, such as density gradient centrifugation or hyperthermia, or biologic approaches, such as incubation with serum containing antilymphoma antibodies or drugs with differential toxicity for lymphoma cells.

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