Improved Prognosis for Patients With Mediastinal Lymphoblastic Lymphoma

By Howard J. Weinstein, Zebulon B. Vance, Norman Jaffe, Donald Buell, J. Robert Cassady, and David G. Nathan

Patients with diffuse lymphoblastic lymphoma (which includes convoluted lymphocytic lymphoma) with mediastinal involvement have predictable progression of disease to a leukemic phase that is cytologically indistinguishable from acute lymphoblastic leukemia (ALL). Therefore we treated 12 patients with diffuse lymphoblastic lymphoma involving the medastinum with therapy that is effective in ALL. Treatment consisted of intermittent combination chemotherapy with adriamycin and preventive central nervous system therapy (craniocervical irradiation and intrathecal methotrexate). Mediastinal irradiation was given either for initial respiratory distress or to patients who had incomplete regression of disease following induction chemotherapy. Eleven patients achieved complete remission. With a median follow-up of 41 mo. and using life table analysis, 86% of these patients have remained in continuous complete remission. The results of this study demonstrate the efficacy of treating diffuse lymphoblastic lymphoma with mediastinal presentation as a disseminated lymphoid malignancy.

The cytologic similarity between acute lymphoblastic leukemia (ALL) and approximately one-third of the childhood non-Hodgkin's lymphomas (NHL) has long been recognized. Barcos and Lukes used the name convoluted lymphocytic lymphoma to describe this subgroup, and more recently Nathwani and associates have recognized both convoluted and nonconvoluted cell types in this subgroup and have classified it as diffuse lymphoblastic lymphoma. Patients with diffuse lymphoblastic lymphoma are predominantly older children and adolescents (increased M:F ratio) who characteristically present with supradiaphragmatic lymphadenopathy (often with mediastinal mass and/or pleural effusion), but who may present with involvement in other nodal or extranodal sites. Although the disease appears localized, there is usually rapid progression to a leukemic phase and/or central nervous system (CNS) involvement. Those patients with mediastinal involvement have the highest likelihood of such progression.

Historically, the survival statistics with radiotherapy alone for children with mediastinal involvement have been dismal. In 1971 Aur and associates published encouraging results in the treatment of childhood lymphoblastic lymphosarcoma with intensive chemotherapy and local radiotherapy. Similar strategy has been used by several investigators, and with the exception of a study by Wollner and

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Submitted October 2, 1978; accepted December 12, 1978.

Supported in part by Grants CA-18662 and CA-19589 from the National Cancer Institute, National Institutes of Health, and by Grant CA-01972 from the National Cancer Institute Research Training Program in Cancer Chemotherapy.

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Blood, Vol. 53, No. 4 (April), 1979 687
associates, the majority of patients with diffuse lymphoblastic lymphoma involving the mediastinum do not remain in complete remission at 1 yr. In 1973 we instituted a treatment protocol for childhood NHL that was known to be effective in childhood ALL. Pathologic material from this study has been reclassified according to the criteria of Nathwani. The results of this protocol for patients with diffuse lymphoblastic lymphoma involving the mediastinum (the group at highest risk for leukemic progression and/or CNS involvement) form the subject of this report.

MATERIALS AND METHODS

Patients

Twelve previously untreated children with mediastinal lymphoblastic lymphoma seen at the Children's Hospital Medical Center, Joint Center for Radiation Therapy, Massachusetts General Hospital, and the Sidney Farber Cancer Institute from December, 1973, to November, 1977, were entered on this study.

After a history was taken, each patient underwent physical examination, complete blood counts, chest x-ray, determination of serum electrolytes and creatinine, liver function tests, urinalysis, and bone marrow aspirate and biopsy. All patients had biopsies for histologic diagnosis, and 4 patients had thoracenteses. Lumbar puncture was performed prior to preventive CNS treatment. Patients with more than 5% lymphoblasts in their bone marrow at diagnosis were considered to have acute leukemia and were not included in this study.

Diagnostic Criteria

Tissue for histologic diagnosis was obtained from biopsies of the mediastinal mass or supradiaphragmatic (cervical, axillary, or supraclavicular) lymph nodes. The criteria of Nathwani and associates were used for diagnosis of lymphoblastic lymphoma. These criteria included a diffuse infiltrative pattern of prolymphocytes and immature lymphoid cells morphologically recognized by the presence of convoluted or nonconvoluted nuclei, fine or dusty nuclear chromatin, indistinct nucleoli, and scanty cytoplasm.

Marker Studies

Biochemical assay of terminal deoxynucleotidyl transferase (TdT) was performed as previously described on total cell homogenates following chromatography through phosphocellulose. TdT determinations were performed on nodal or mediastinal mass tissue obtained at initial diagnostic biopsy in 4 patients.

Viable lymphocytes in suspension from 4 patients were examined for cell surface immunoglobulin by direct immunofluorescence and spontaneous rosette formation with sheep erythrocytes as previously described or for reactivity to anti-p23,30 and anti-HTL (human thymocyte) sera as previously described.

Treatment

Remission-induction therapy included adriamycin (A), prednisone (P), and vincristine sulfate (O) (Fig. 1). At diagnosis, 5 patients received 500-1200 rads (over 2-4 days) to the mediastinum as emergency treatment for upper airway compression or superior vena cava syndrome. Following induction of remission, patients were reevaluated for evidence of residual tumor, with repetition of previously abnormal staging studies. Patients in whom there was complete regression of all measurable tumor were defined as having achieved complete remission (CR).

Consolidation included a 5-day course of chemotherapy (adriamycin with vincristine on day 1, and 6-mercaptopurine and prednisone on days 1-5) followed in 1 wk by five doses of asparaginase administered every other day (Fig. 1).

Preventive CNS therapy consisted of cranioeervical radiation from a 4-MeV linear accelerator delivering 2400 rads in 13 fractions over 17 days to portals previously described. Five doses of intrathecal methotrexate (12 mg/sq m) were given within the same time span. Maintenance intrathecal methotrexate was given every 18 wk after completion of preventive CNS therapy (Fig. 1). The first patient (case 1) entered on study did not receive preventive CNS therapy.
Fig. 1. Non-Hodgkins Lymphoma Schema (APO). Protocol design (APO), schematic: ADR, Adriamycin, 30 mg/sq m intravenously; VCR, vincristine, 2.0 mg/sq m (maximum 2.0 mg) intravenously; 6MP, 6-mercaptopurine, 225 mg/sq m/day × 5 days, orally; Pred, prednisone, 120 mg/sq m/day × 5 days orally; L-asparaginase, 56,000 IU/sq m/dose for patients under 6 yr old, 28,000 IU/sq m/day for patients over 6 yr old, intravenously; Mtx, methotrexate, 7.5 mg/sq m/day × 5 days, intravenously day 1, intramuscularly days 2–5; I.T. Mtx, intrathecal methotrexate, 12 mg/sq m (maximum 12 mg). Cranial radiation: 2400 rads/13 fx/17 days.
Treatment in remission involved 5-day courses of chemotherapy (adriamycin and vincristine on day 1, and 6-mercaptopurine and prednisone on days 1–5) given every 3 wk. After completion of a total adriamycin dose of 450 mg/sq m, the adriamycin was replaced by parenteral methotrexate for the duration of treatment (Fig. 1). Dose adjustments of all chemotherapeutic agents were designed to permit administration of maximally tolerated doses of myelosuppressive agents. Chemotherapy was electively discontinued after 2 yr of continuous disease-free survival from initial treatment.

The duration of remission (continuous disease-free survival) was measured from the time of initial therapy. Statistical analysis was by the life table method.

RESULTS

The 12 patients entered on study from December, 1973, to November, 1977, were evaluable for analysis. There were 9 males and 3 females with a median age of 11 yr (range 2.5–22 yr). Their clinical characteristics are outlined in Table 1. All 4 patients tested for terminal transferase had positive assays. Four patients had surface marker analyses of their tumor cells. These patients had T-cell surface markers (E- or HTL-positive, Table 2).

Eleven of 12 patients achieved CR with APO chemotherapy (with or without radiotherapy) (Table 1). One patient (case 8) was an induction failure. Of note was this patient’s failure to take prednisone during remission induction. He subsequently achieved CR with a secondary protocol comprising COAP (cyclophosphamide, vincristine, cytosine arabinoside, and prednisone) and mediastinal irradiation. He remains in remission on COAP maintenance therapy for 17 mo.

The only relapse occurred in a patient (case 7) who had asymptomatic meningeal lymphoma detected by routine cerebrospinal fluid (CSF) examination prior to receiving preventive CNS therapy. His CSF blasts cleared during CNS treatment (craniocervical irradiation and intrathecal methotrexate), but he subsequently had a concurrent CNS and testicular relapse. He achieved a second remission with intrathecal methotrexate and testicular irradiation and has remained in remission.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Additional Sites of Involvement</th>
<th>Response</th>
<th>Remission Duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>F</td>
<td>Pleural effusion</td>
<td>CR+</td>
<td>54+</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>M</td>
<td>Lung, pleural effusion</td>
<td>CR</td>
<td>52+</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>F</td>
<td>Pleural and pericardial effusions</td>
<td>CR</td>
<td>51+</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>Cervical, supraclavicular lymphadenopathy</td>
<td>CR</td>
<td>44+</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>M</td>
<td>Cervical, supraclavicular lymphadenopathy</td>
<td>CR</td>
<td>43+</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>F</td>
<td>Pericardium, splenomegaly</td>
<td>CR</td>
<td>39+</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>M</td>
<td>Supraclavicular lymphadenopathy, CNS</td>
<td>CR†</td>
<td>20 (CNS and testicular relapse)</td>
</tr>
</tbody>
</table>

8    | 4   | M   | Pleural effusion, splenomegaly  | IF       | §                        |
9    | 2½  | M   | Cervical lymphadenopathy, pleural effusion | CR | 16+                     |
10   | 7   | M   | Cervical lymphadenopathy, pleural effusion | CR | 11+                     |
11   | 15  | M   | Skin nodules                    | CR       | 9+                      |
12   | 22  | M   | Cervical lymphadenopathy        | CR       | 7+                      |

*CR, complete remission; IF, induction failure.
†Received concurrent mediastinal irradiation and APO.
‡Required mediastinal irradiation for CR.
§Entered CR with mediastinal irradiation and COAP and is disease-free for 17 mo.
Table 2. Cell Surface and Biochemical Marker Analyses

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Site of Biopsy</th>
<th>Sig</th>
<th>E</th>
<th>HTL</th>
<th>p23,30</th>
<th>TdT</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Mediastinum</td>
<td>ND†</td>
<td>ND</td>
<td>+</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Cervical node</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>Mediastinum</td>
<td>9</td>
<td>86</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>Mediastinum</td>
<td>2</td>
<td>72</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
</tr>
</tbody>
</table>

*Results of Sig (surface immunoglobulin) and E receptors for sheep erythrocytes are expressed as percentage of positive cells. TdT-positive samples contained 1.4–3.5 units TdT/10^6 cells. HTL and p23,30 positivity refers to majority of cells demonstrating immunofluorescence with anti-HTL and anti-p23,30 sera on a fluorescence-activated cell sorter.
†ND, not done.

on high-dosage methotrexate and cytosine arabinoside maintenance therapy for 20 mo.

With a median follow-up of 41 mo (range 7–54 mo), and using life table analysis, 86% of 11 patients who achieved CR with APO (with or without radiotherapy) have remained in continuous CR (Fig. 2, disease-free). All 12 patients are surviving without evidence of disease.

Six patients had therapy discontinued after 22–24 mo in CR, and they have been followed for a median of 24 mo off therapy. All 6 patients remain disease-free.

Toxicity

The therapeutic regimen was well tolerated. All toxicity was reversible. All patients had alopecia and minimal to moderate nausea and vomiting associated with the pulses of chemotherapy throughout the treatment course. There was one hospitalization per patient during the 2-yr treatment course for fever or infection associated with neutropenia (< 1000 neutrophils/cu mm). Three children had esophagitis during or shortly following induction therapy, and this was attributed to adriamycin and radiation interactions. Three patients developed localized herpes

Fig. 2. Life table probabilities of survival and disease-free survival according to time since initial therapy. Each tick represents a patient.
zoster during treatment. One patient had a Guillain-Barre syndrome during treatment, with subsequent full recovery of neurologic function. There was no overt cardiac toxicity noted during the 2 yr of treatment or during subsequent follow-up.

**DISCUSSION**

The present study demonstrates the efficacy of a leukemia-like treatment approach for mediastinal lymphoblastic lymphoma. In the past, local control of mediastinal lymphoblastic lymphoma was attained by the use of radiation.\(^6\),\(^7\) However, most patients relapsed in the bone marrow, gonads, or CNS. Several postmortem examinations revealed that the mediastinum remained free of disease in the presence of widespread infiltration of other organs. This relapse pattern suggested that occult disseminated disease was present at diagnosis.

Several recent programs combining radiation and combination chemotherapy have been used in the treatment of childhood NHL.\(^9\),\(^10\) Despite this approach, the majority of patients with mediastinal lymphoma relapsed systemically within 1 yr of diagnosis. Wollner and associates reported an 88% actuarial survival for children with mediastinal NHL treated with a modification of their ALL protocol called LSA2-L2.\(^11\) This is the only other study with results that appear to be as good as those achieved with APO.

A number of treatment variables may have contributed to the excellent results of the APO program. In the first place, adriamycin is employed for both remission induction and maintenance therapy. Adriamycin is used because early clinical trials have indicated that adriamycin has significant activity in malignant lymphoma.\(^2\) Secondly, in addition to systemic combination chemotherapy, patients received preventive CNS therapy because we approach treatment of mediastinal lymphoblastic lymphoma as though it were a form of ALL. As in ALL, the CNS has been reported to be the initial site of relapse in 10%–50% of children with mediastinal NHL.\(^4\),\(^12\) The only CNS relapse in this study occurred in a patient who had asymptomatic meningeal disease (positive cytocentrifuge) prior to receiving preventive CNS therapy. Finally, mediastinal radiation did not compromise initial chemotherapy. The role of mediastinal irradiation as an adjuvant to combination chemotherapy for the treatment of mediastinal lymphoblastic lymphoma is uncertain. Mediastinal irradiation ( 2000 rads) was delivered to only 3 of 12 patients in this study. Because of the nonessential role of irradiation in the majority of these patients, plus the known toxicity of adriamycin-irradiation interaction, we recommend local mediastinal irradiation for initial respiratory distress or vascular obstruction or when there is evidence of incomplete regression or progression of mediastinal disease with chemotherapy alone.

In this study the diagnosis of diffuse lymphoblastic lymphoma was based on the morphologic criteria of Nathwani.\(^3\) More recently, Donlon and associates have consistently found TdT in diffuse lymphoblastic lymphomas, and this biochemical marker may prove to be a valuable diagnostic aid.\(^2\) The four cases assayed for TdT in this study were positive. The significance of convoluted lymphocytes and/or a positive acid phosphatase reaction in lymphoblastic lymphomas remains uncertain.\(^2\)

The precise relationship between ALL with a mediastinal mass and mediastinal lymphoblastic lymphoma is not established. It has been postulated that ALL
associated with a mediastinal mass is a more advanced stage of mediastinal lymphoblastic lymphoma. This would be analogous to the pathogenesis of thymic lymphoma in AKR mice, in which tumor originates in the thymus and then disseminates to the spleen, liver, peripheral blood, and bone marrow.

In a child with ALL and a mediastinal mass, the associated clinical characteristics and the cell surface markers of the blasts are indistinguishable from analogous findings for childhood mediastinal lymphoblastic lymphoma. In both diseases there is a predominance of adolescent males, and the malignant cells usually have T-cell surface markers. Lymphoblasts from the 4 patients analyzed in our study had T-cell surface markers (Table 2).

ALL with a mediastinal mass and mediastinal lymphoblastic lymphoma have been arbitrarily separated by the presence or absence of overt bone marrow involvement at diagnosis. Patients with bone marrow involvement at diagnosis (T-cell ALL) have, in our experience (with similar therapy) and in that of others, a poor prognosis. Yet we observed excellent results in patients with mediastinal lymphoblastic lymphoma. This survival difference may be related only to tumor burden at diagnosis (occult versus overt bone marrow involvement for mediastinal lymphoblastic lymphoma and T-cell ALL, respectively) or to unknown biologic differences between these diseases. Future studies will undoubtedly deal with these questions.

In summary, we have demonstrated the efficacy of combination chemotherapy with adriamycin and preventive CNS therapy for the treatment of mediastinal lymphoblastic lymphoma. Although the mediastinum is most often the presenting site of disease in patients with diffuse lymphoblastic lymphoma, both nodal and extranodal primaries are not infrequent. Therefore our treatment program may have relevance for a larger group of patients.

ACKNOWLEDGMENT

We are indebted to Dr. R. McCaffrey for performing terminal transferase assays, to Drs. S. Schlossman, J. Long, and A. Aisenberg for cell surface marker studies, to Dr. M. Fosburg for treatment of Massachusetts General Hospital patients, to Dr. G. Canellos for a careful review of the manuscript, and to Margie O’Malley-Keyes for secretarial assistance.

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