Lymphoblastic Lymphoma in Adults: Results of a Pilot Protocol

By C. Norman Coleman, James R. Cohen, Jerome S. Burke, and Saul A. Rosenberg

Thirteen adult patients with histologically confirmed lymphoblastic lymphoma were treated with an intensive chemotherapy program consisting of induction with cyclophosphamide, Adriamycin, vincristine, and prednisone (modified CHOP); consolidation and central nervous system (CNS) prophylaxis with methotrexate intrathecally and by high-dose intravenous injection, citrovorum factor and L-asparaginase; reinforcement with CHOP; and maintenance with 6-mercaptopurine and methotrexate. Treatment duration was 1 yr. A 14th patient with T-cell acute lymphoblastic leukemia was also treated at presentation by the same regimen. Thirteen patients had at least a mediastinal mass or abnormal cells in the bone marrow.

LYMPHOBLASTIC LYMPHOMA is a recently defined subgroup of the diffuse non-Hodgkin's lymphomas. The cells are morphologically indistinguishable from the blast cells of acute lymphocytic leukemia (ALL) and are predominately T cells. The disease occurs principally in adolescent males, and approximately half the patients present with a mediastinal mass. Bone marrow involvement is present at diagnosis in 25%–30% of patients and in 80% of patients during the course of the disease; central nervous system relapses are common. Unlike patients with ALL, thrombocytopenia is infrequent in patients with lymphoblastic lymphoma. Lymphoblastic lymphoma has many similarities to T-cell ALL, which comprises 25% of the cases of ALL and some consider lymphoblastic lymphoma and T-cell ALL to be variants of one disease. T-cell ALL is characterized by an initial high white count and mediastinal masses in half the patients. Although the complete response rate to therapy is similar for T-cell and non-T-cell ALL, many more patients relapse with T-cell ALL. Frei and Sallan reported a 0% 3-yr relapse-free survival, with extramedullary sites accounting for half of the relapses, in patients with T-cell ALL. In the St. Jude ALL Study VIII, testicular relapse was eight times more common in males with mediastinal masses. Central nervous system (CNS) relapses were also common in their patients with mediastinal masses. Thus, lymphoblastic lymphoma, T-cell ALL, or “high-risk” ALL have many common clinical characteristics.

Prior to the realization that lymphoblastic lymphoma was a separate entity, it was often called diffuse poorly differentiated lymphocytic lymphoma, diffuse histiocytic lymphoma, or diffuse undifferentiated lymphoma and was treated with local irradiation and/or cyclic chemotherapy using drugs such as cyclophosphamide, Adriamycin, vincristine, and prednisone. In the report by Nathwani et al., the median survival was 8 mo, with no patients living beyond 26 mo. Rosen et al. reported a median survival of 13 mo in 12 adults with convoluted lymphocytic lymphoma. They reported that responses were dramatic and remissions were brief, although two patients had prolonged survival (24+ and 44+ mo). Our previous results in nine adult patients with lymphoblastic lymphoma, treated with either radiotherapy or pulse chemotherapy and without CNS prophylaxis, yielded a median survival of 6 mo with only one patient remaining free of disease. (unpublished data). Various groups, particularly those treating pediatric patients, began using ALL-like protocols for those patients, incorporating more aggressive and continuous induction therapy, CNS prophylaxis, and prolonged maintenance. Our protocol was initiated in 1977 and incorporated high-dose methotrexate as part of the systemic program and CNS prophylaxis based on preliminary data reported in leukemic patients, and based in part on its activity in childhood non-Hodgkin’s lymphomas. Cranial irradiation was omitted to reduce the risk of neurologic dysfunction and leukoencephalopathy. Recent studies have found evidence of abnormali-
ties on computerized tomographic brain scans in 50% of patients treated with brain irradiation and high-dose methotrexate.\textsuperscript{13}

MATERIALS AND METHODS

Fourteen patients were entered on this protocol. Table 1 shows their clinical features, including the stage using the Ann Arbor system\textsuperscript{14} and the system described by Murphy\textsuperscript{15} for childhood non-Hodgkin's lymphomas. The major difference from the Ann Arbor system is that the presence of mediastinal or unresectable abdominal disease is considered stage III. All of our stage III patients had mediastinal masses, as did four of six stage IV patients (in total 11/14 patients had mediastinal masses). The median age of patients was 22 yr (range 16-50) and the male-female ratio was 2.5:1. Staging procedures included a chest x-ray, lymphangiogram (10/14 patients), routine blood studies, biopsy of the primary lesion, bone marrow biopsy, and lumbar puncture. Cell typing of the lymphocytes was not routinely available.

On review, patient 13 was felt to have two malignancies at the time of presentation—lymphoblastic lymphoma and chronic myelogenous leukemia (CML). His case is discussed in detail below and his data are included in the actuarial analysis. An additional patient (14) had CNS disease at presentation. His clinical course is presented but he is excluded from survival analysis.

The treatment schema is shown in Fig. 1. Actuarial curves were calculated by the method of Kaplan and Meier.\textsuperscript{16}

RESULTS

All cases of lymphoblastic lymphoma had a diffuse pattern of tissue infiltration. Cytologically, the malignant cells were characterized by sparse cytoplasm, relatively uniform intermediate sized nuclei with finely dispersed chromatin, inconspicuous nucleoli, and complex convoluted nuclear membranes. The convolutions were prominent in 11 cases; the lymphoblasts in the remaining 3 cases were predominantly nonconvoluted. In these cases, however, rare convoluted cells could also be found but were only discovered after prolonged search, frequently with the aid of oil immersion. Mitotic figures were abundant in all cases with as many as four mitoses per high power field. One case showed a starry sky pattern.

The tissues from which the diagnoses were established were peripheral lymph nodes in six cases and mediastinal masses in another three. Only one case showed partial lymph node involvement with sparing of germinal centers and localization of the malignant infiltrate in the paracortical or T-cell area of the node. Four additional patients presented with involvement of Waldeyer's ring or soft tissues of the oropharynx, and these sites subsequently were documented by biopsy. The remaining patient (10) was diagnosed solely from the bone marrow biopsy and clot section. In this patient, the marrow cellularity was 100% and replaced by a diffuse infiltrate of convoluted lymphoblasts with absence of normal hematopoietic elements. Four other patients also had evidence of marrow involvement at the time of initial diagnosis, but the degree of marrow replacement by malignant cells varied from 5% to 80% (see Table 1). Residual normal hematopoietic elements could be discerned in these cases.

All patients had a complete clinical response. Pathologic complete response was documented in all cases with bone marrow involvement. The median follow-up for the entire group is 19 mo (range 2-40 mo). Ten patients completed the planned therapy; six of them

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Stage</th>
<th>Medast.</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>I A</td>
<td>I</td>
<td>NED 25 mo</td>
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<tr>
<td>2</td>
<td>F</td>
<td>28</td>
<td>III A</td>
<td>III</td>
<td>Induction death — 2 mo; NED at autopsy</td>
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<tr>
<td>3</td>
<td>F</td>
<td>20</td>
<td>III B</td>
<td>III</td>
<td>CNS relapse — 2 mo; died with disease 8 mo</td>
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<tr>
<td>4</td>
<td>M</td>
<td>17</td>
<td>III B</td>
<td>III</td>
<td>CNS relapse — 2 mo; died with disease 15 mo</td>
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<tr>
<td>5</td>
<td>M</td>
<td>45</td>
<td>II A</td>
<td>III</td>
<td>DID, NED — 4 mo</td>
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<tr>
<td>6</td>
<td>M</td>
<td>19</td>
<td>II A</td>
<td>III</td>
<td>NED — 17 mo</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>17</td>
<td>II A</td>
<td>III</td>
<td>NED — 21 mo</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>26</td>
<td>II A</td>
<td>III</td>
<td>NED — 37 mo</td>
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</table>

**Table 1. Patient Population and Clinical Features**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Stage</th>
<th>Medast.</th>
<th>Course</th>
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<tr>
<td>9†</td>
<td>M</td>
<td>21</td>
<td>IV A</td>
<td></td>
<td>CNS relapse — 15 mo; NED — 26 mo</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>23</td>
<td>IV A*</td>
<td>+</td>
<td>198.0 34 100 NED — 19 mo</td>
</tr>
<tr>
<td>11†</td>
<td>F</td>
<td>43</td>
<td>IV A</td>
<td>—</td>
<td>7.7 468 15 Nodal relapse — 23 mo; alive — 27 mo</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>20</td>
<td>IV B</td>
<td>+</td>
<td>20.0 155 80 NED — 40 mo</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>16</td>
<td>IV B</td>
<td>+</td>
<td>5.7 235 5 DID — CML</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>47</td>
<td>IV CM A*</td>
<td>+</td>
<td>18 mo</td>
</tr>
</tbody>
</table>

NED, no evidence of disease; DID, dead of intercurrent disease; WBC, white blood count (\( \times 1000 \)); PLT, platelet count (\( \times 1000 \)).

*No lymphangiogram done.
†Protocol violation during CNS phase.
<table>
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<tr>
<th>WEEK</th>
<th>INDUCTION</th>
<th>CONSOLIDATION</th>
<th>REINFORCEMENT</th>
<th>MAINTENENCE</th>
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<td>1 2 3 4 5 6 7</td>
<td>8 9 10 11 12 13 14 17 20 23</td>
<td>14 17 20 23</td>
<td>52</td>
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<tr>
<td>CYTOXAN 400 mg/m² x 4 PO</td>
<td></td>
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<tr>
<td>ADRIAMYCIN 50 mg/m² IV</td>
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<tr>
<td>VINCRIKTE 2 mg IV</td>
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<tr>
<td>PREDNISONE 40 mg/m² PO</td>
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<td>CNS Phase x 5 weeks</td>
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<td>L-ASPARAGINASE 6000 u/m² IM</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IT MTX 12 mg/m²</td>
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<tr>
<td>HD MTX 1 gm/m²</td>
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<tr>
<td>24° - CF 25 mg/m² q6h x 3 days</td>
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<td></td>
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<tr>
<td>6 mp - 75 mg/m² P.O.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX - 30 mg/m² P.O.</td>
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</table>

Fig. 1. Treatment schema. CNS phase, repeated weekly 5 times; MTX, methotrexate; IT, intrathecal by Lumbar puncture; HD, high-dose bolus; CF, citrovorum factor; 6MP, 6 mercaptopurine—orally.

are alive and well 5-28 mo after cessation of therapy. Only two patients remain under treatment, both for relapse (9 and 11).

Four patients have subsequently relapsed, three having their primary site of relapse in the CNS. Two of the latter patients presented at relapse with cranial nerve abnormalities and one presented with headaches and papilledema. Of the CNS relapses, one occurred 1 wk before the planned initiation of CNS prophylaxis; one occurred at 6 mo, during the reinforcement phase; and one occurred at 15 mo, 3 mo after discontinuation of therapy. The latter patient had a major protocol violation in that intrathecal methotrexate (IT-MTX) was given shortly before initiation of citrovorum factor rescue (CFR), rather than 24 hr earlier. The fourth patient has recently experienced a clinical relapse with the appearance of an abdominal mass and generalized lymphadenopathy 11 mo after therapy was discontinued. Unfortunately, this patient was lost to follow-up shortly after completion of the consolidation phase, and the patient's compliance with the maintenance program is questionable.

One patient who was included in the treatment protocol presented with mediastinal lymphoblastic lymphoma and probable concomitant chronic myeloid leukemia. The patient, a 17-yr-old Latin American male, presented with pyrexia, massive lymphadenopathy, and splenomegaly. A chest x-ray revealed mediastinal enlargement, but the peripheral blood was unremarkable except for a few bands. A lymph node biopsy demonstrated typical diffuse lymphoblastic lymphoma with rare convolutions; a naphthol AS-D chloroacetate esterase (NASDCA) stain was negative. On biopsy, the bone marrow was packed due to a proliferation of granulocytes in all stages of maturation, including myeloid cells with dysplastic features; erythroid and megakaryocytic elements were markedly decreased. In addition, one small area comprising less than 5% of the marrow cellularity showed, upon review, a small nidus suggestive of focal involvement by lymphoblastic lymphoma. Lymphoblastic lymphoma was not demonstrated in subsequent marrow studies performed over the following 16 mo. These marrow biopsies and aspirations, however, continued to demonstrate chronic myeloid leukemia, including one specimen with a definite myeloid blast crisis; the NASDCA stain was positive. At that time the white blood cell count had increased to $200 \times 10^9$ liter with 5% myeloblasts as well as numerous eosinophils and basophils. The leukocyte alkaline phosphatase score was low, but the
results of cytogenetic studies were not available due to technical factors. This patient died of chronic myeloid leukemia, which became clinically active at the conclusion of the maintenance phase. For actuarial calculations he is considered to have died from intercurrent disease.

At present there have been five deaths—one induction death due to sepsis; two deaths among the three patients with CNS relapses; one death probably related to asparaginase toxicity (v.i.); and the one death due to chronic myelogenous leukemia. Actuarial relapse-free survival and survival curves for the 13 patients are shown in Fig. 2. The results at 3 yr are: relapse-free survival, 56%; survival, 61%.

The patient who presented with CNS disease had complete disappearance of disease but relapsed in the CNS at 8 mo; he later relapsed systemically and died 10 mo after the date of diagnosis. Of the five patients with initial bone marrow involvement, one relapsed in the CNS but had a major protocol violation during CNS prophylaxis. A second bone marrow positive patient recently relapsed systemically, and a third patient died of CML.

Hematologic toxicity was severe with half the patients developing a white blood count nadir of less than 100/cumm during induction. As indicated, one patient died of infection during induction. The cycle was lengthened to 4 wk in two-thirds of the patients during reinforcement because of leukopenia. The CNS prophylaxis phase was well tolerated with only 20% of courses requiring modification due to low white counts (high-dose MTX was delayed for WBC < 2000). One death occurred during CNS consolidation. This patient (5) developed hyperglycemia (glucose, 700) during l-asparaginase therapy. This was controlled with insulin and another dose of l-asparaginase was given. He returned home, developed seizures and coma, and could not be resuscitated at his local hospital. His presenting laboratory studies at his local hospital included a normal white count, a blood glucose of 452, a normal electrolyte panel, and normal arterial pH. No autopsy data were available, but he had been clinically free of disease, including a normal lumbar puncture, during the week prior to his death.

**DISCUSSION**

Our population of 14 adult patients included 11 patients with mediastinal masses, 5 with involvement of the bone marrow and 1 with CNS disease. All met the criteria of lymphoblastic lymphoma as described by Nathwani, except one patient who had no tissue biopsied except bone marrow. This patient had leukemic cells in the peripheral blood that were typed as T cells; therefore, he could be designated as having T-cell ALL, which in general is felt to have a poor prognosis except for one recent study suggesting improved results.

Although lymphoblastic lymphoma has been reported in adults, there are as yet no other series published with systematic treatment given to all patients. Therefore, our data are best compared with the results of three pediatric groups: St. Jude Children’s Hospital, Sidney Farber Cancer Institute (SFCI), and Memorial Sloan-Kettering (MSK). It is difficult to draw precise comparisons, however, since staging systems differ, and childhood non-Hodgkin’s lymphomas represent a heterogeneous group of histologic subtypes and clinical presentations.

The SFCI has reported results of therapy for mediastinal lymphoblastic lymphoma using a 24-mo treatment program and incorporating central nervous system (CNS) prophylaxis of intrathecal methotrexate (IT MTX) and cranial irradiation commencing on week 7 of therapy. Their update with a median follow-up of 20 mo, includes complete responses in 18 of 19 patients. On actuarial analysis, 63% of the complete responders (59% of the total group) remain in complete remission. The actuarial survival of all patients is 87%; 4 relapses have occurred, 2 involving the CNS. Murphy and Hustu recently reported the data on the results of treatment from St. Jude. CNS prophylaxis consisting of cranial irradiation and IT MTX reduced the rate of CNS relapse. However, many relapses occurred before the onset of prophylaxis at week 7. Their advanced stage patients (Murphy stage III and IV) at 2 yr had an actuarial freedom from relapse of 38% and survival of 55%. Wollner et al. from MSK have achieved a 61% freedom from
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Relapse at 5 yr for patients with lymphoblastic lymphoma treated by the LSA1L2 protocol, which incorporates only IT MTX for CNS prophylaxis but commences this drug at week 1. A prior report from this group\(^2\) stated that CNS relapse occurred in 16% of patients.

It appears that CNS prophylaxis is effective, yet must be given early in the program. Our protocol failed in the CNS in three patients—one before prophylaxis and two after. One patient with a positive bone marrow incorrectly received CF rescue at the same time as IT MTX. Since reduced folates readily cross into the CNS, this patient’s CNS prophylaxis may well have been ineffective.\(^2\)

Methotrexate as administered by this protocol differs from its use in regimens from other groups. Intrathecal MTX alone, at a dose of 12 mg/sqm can achieve CSF levels of 10 \(^6\)M for 24 hr,\(^11\) but it is not reproducible and may be unevenly distributed in the ventricles.\(^2\) RPMI\(^10\) used an i.v. infusion of 500 mg/sqm given \(\frac{1}{2}\) as a bolus, and \(\frac{1}{2}\) as a 24-hr infusion along with IT MTX at 12 mg/sqm. The infusion itself gives lumbar CSF levels of \(\approx 10 \) \(^6\)M, and this is raised to 10 \(^6\)M-10 \(^7\)M for 24 hr when i.v. and IT MTX are both given. Our method would give an estimated peak plasma level of 6.7 \(\times\) 10 \(^7\)M for a bolus of 1 g/sqm.\(^2\)

Based on a plasma methotrexate half-life of 2–3 hr for most of the first day, the plasma level would be \(\approx 10 \) \(^6\)M for 12–18 hr. With methotrexate infusions, the CSF drug level is 1/10 to 1/100 that of the plasma level, therefore, we estimate that our CSF level was between 10 \(^4\)M and 10 \(^5\)M for at least 12 hr, although no levels were assayed. Incorporation of uridine by human leukemic cells was inhibited by methotrexate concentrations of 10 \(^6\)M, but this did not correlate with remission induction.\(^2\) Freeman et al.\(^11\) reported that a cerebrospinal fluid MTX level of 10 \(^7\)M yielded a decrease in the number of blasts in 3 of 5 patients with central nervous system leukemia.

It is therefore not possible from our study to conclude that CNS prophylaxis with high-dose and IT MTX is not as effective as cranial irradiation and IT MTX, as methods of administration of MTX can vary greatly. Since three of our four failures were in the CNS, we have revised our protocol and initiate CNS prophylaxis earlier and utilize cranial irradiation and IT MTX. A comparison of results of these studies will hopefully yield information as to the better method of CNS prophylaxis.

Of the five deaths in this group of patients, two were drug related, two were due to CNS relapse, and one was considered due to an intercurrent disease. This latter patient, from South America, relapsed with chronic myelogenous leukemia, which had been diagnosed simultaneously with lymphoblastic lymphoma. Unfortunately, during Ph\(^1\) chromosome analysis, the specimen was mishandled and a repeat study could not be obtained. Kjeldsberg et al.\(^2\) have described lymphoblastic lymphoma terminating in AML in three patients. Hutter et al.\(^2\) described two patients with lymphoid malignancies, one with ALL and one with lymphoblastic lymphoma, whose diseases at relapse had myeloid features. Other recent reports\(^2\) have described cases of ALL terminating in CML with blast crisis. Our patient had a concomitant presentation of lymphoblastic lymphoma and CML and is clearly analogous to the other patients recently reported with both lymphoid and myeloid malignancies.\(^2\)

Although cytogenetic, enzymatic, and cell surface marker studies were not performed in our patient, the clinical and pathologic data suggest that this case probably represents another example of a malignancy that conforms to the current hypothesis of origin in a pluripotential stem cell with the capacity for synchronous lymphoid and myeloid expression.\(^2\)

The hematologic toxicity of this drug regimen was severe. The 100% complete response rate may be due to the high doses of drug used. Only one patient was purposely given two-thirds doses by his physician and has remained free of disease. Our new protocol will use somewhat lower doses of drug. In leukemia it appears that rapid cytoreductive therapy is important\(^8\) and it remains to be seen whether the high response rate will be maintained with lower drug doses and less toxicity.

These results, 3-yr survival of 61% and relapse-free survival of 55%, are in contrast to the short median survival we and others\(^2\) experienced in the past using lymphoma-type pulse chemotherapy without CNS prophylaxis. This pilot study shows that an aggressive ALL-like protocol is successful in treating adult lymphoblastic lymphoma patients and yields results similar to those obtained in the treatment of childhood lymphoblastic lymphoma. High-dose MTX with CF rescue as used in this protocol failed to prevent CNS relapse in 3 of 13 patients. Drug toxicity led to two deaths. Our current modified protocol (1) uses early CNS prophylaxis, (2) includes cranial irradiation and IT MTX, (3) omits high-dose MTX, and (4) lowers the dose of cyclophosphamide. Routine use of lymphocyte markers will be done to type the cells. It remains to be seen how treatment results from our modified protocol and those from other adult populations compare to the results of this study.

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REFERENCES

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