Improved Results of Treatment of Adult Acute Lymphoblastic Leukemia

By Charles A. Linker, Lee J. Levitt, Margaret O’Donnell, Curt A. Ries, Michael P. Link, Stephen J. Forman, and Mark J. Farbstein

We designed a treatment program to improve the outcome for adults with acute lymphoblastic leukemia (ALL). Treatment included a remission-induction phase followed by intensive alternating cycles of non-cross-resistant chemotherapy and prolonged oral maintenance therapy. Eighty-one consecutive previously untreated patients were entered on this study. Ninety-four percent of patients entered complete remission. A Kaplan-Meier analysis predicted that 53% ± 9% (SEM) of patients in remission will remain free of disease at 3 years. Neither age, sex, WBC count, nor immunophenotype had a significant effect on remission duration. This program of intensive cyclical chemotherapy has improved the disease-free survival of patients with adult ALL.

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MATERIALS AND METHODS

Patients. Eighty-one consecutive adults with ALL aged <50 years who were seen either at the University of California at San Francisco, City of Hope National Medical Center, Stanford University Medical Center, or by collaborating private physicians in the Bay Area Leukemia Study Group, entered this study between October 1980 and March 1984. During the first 16 months of the study, patients were entered only from the University of California at San Francisco, but beginning in February 1982, patients were entered from all centers. Patients were either previously untreated or had received <2 weeks of therapy with vincristine and prednisone. Patients were diagnosed as having ALL if morphology was compatible with that diagnosis, if histochemical stains for both peroxidase and α-naphthyl butyrate esterase were negative, and if lymphoid markers could be demonstrated. All patients had >50% blasts in the bone marrow. Immunophenotyping was performed by indirect immunofluorescent techniques using reagents and methods as previously described. The marker used to establish lymphoid lineage was terminal deoxynucleotidyl transferase (TdT) in 72 patients, common ALL antigen (CALLA) in 5 patients, T cell antigen (Leu 1 and Leu 9) in 3 patients, and B cell antigen (BA-1) in 1 patient. Patients were excluded because of prior therapy, presence of Philadelphia chromosome, age >50 years, or diagnosis of B cell leukemia based on L3 morphology and presence of surface immunoglobulin. Central nervous system disease was defined as the presence of any lymphoblasts in cerebrospinal fluid.

Treatment. All patients gave informed consent according to guidelines approved by each institution’s Committee on Human Research. Chemotherapy was given in three phases: a remission-induction phase, an intensive alternating combination chemotherapy phase, and a low-dose oral maintenance phase. Remission was induced with daunorubicin, vincristine, and L-asparaginase (Table I). Patients not entering complete remission after 6 weeks of induction chemotherapy were considered to have failed treatment and were taken off study.

Central nervous system prophylaxis was initiated within 1 week of achievement of complete remission. Eighteen hundred rad of cranial radiation were delivered in ten fractions over 12 to 14 days. Six weekly doses of 12 mg of intrathecal methotrexate were administered concurrently. Patients with CNS involvement at diagnosis began their weekly intrathecal methotrexate during induction chemotherapy and received 10 weekly doses. Thereafter, these high-risk patients received intrathecal methotrexate monthly during

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Table 1. Remission Induction Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Days</th>
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<tbody>
<tr>
<td>Daunorubicin</td>
<td>50 mg/m² IV</td>
<td>1-3</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg IV</td>
<td>1, 8, 15, 22</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² PO</td>
<td>1-28</td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>6,000 U/m³ IM</td>
<td>17-28</td>
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If bone marrow on day 14 has residual leukemia:
- Daunorubicin 50 mg/m², day 15

If bone marrow on day 28 has residual leukemia:
- Daunorubicin 50 mg/m² IV, days 29-30
- Vincristine 2 mg IV, days 29-36
- Prednisone 60 mg/m² PO, days 29-42
- L-Asparaginase 6,000 U/m³ IM, days 29-35

IV, intravenously; PO, orally; IM, intramuscularly.

the first year of therapy, and the dose of cranial radiation was increased to 2,800 rad.

Courses 1, 3, 5, and 7 of consolidation chemotherapy consisted of daunorubicin, vincristine, prednisone, and L-asparaginase (Table 2). Courses 2, 4, 6, and 8 of consolidation chemotherapy consisted of VM-26 and Ara-C. Courses of consolidation chemotherapy were given approximately monthly after the neutrophil count had risen to >1,000/μL and the platelet count to >100,000/μL. The ninth consolidation course consisted of moderate-dose methotrexate and leucovorin rescue.

Maintenance chemotherapy consisted of methotrexate 20 mg/m² orally weekly and 6-mercaptopurine 75 mg/m² orally daily. Oral maintenance therapy was continued until 30 months of continuous complete remission; all therapy was then discontinued.

Criteria for response. Patients were considered to be in complete remission when the neutrophil count was >1,500/μL, platelet count was >150,000/μL, and results of bone marrow examination were normal. In addition, patients had to be afibrile and have a normal performance status. Mediastinal masses, peripheral lymphadenopathy, and other extramedullary disease had to have completely resolved.

Supportive care. During remission-induction therapy, patients received prophylactic oral nystatin or clotrimazole, as well as trimethoprim-sulfamethoxazole. The trimethoprim-sulfamethoxazole was continued until 30 months of continuous complete remission. Episodes of fever and neutropenia were treated with broad-spectrum antibiotics, usually an aminoglycoside and a semisynthetic penicillin. Platelet transfusions were given prophylactically to maintain the platelet count >10,000/μL, and RBC transfusions were given according to standard transfusion practice. Granulocyte transfusions were not used.

Statistical analysis. The duration of remission was measured from the time of the remission-bone marrow examination. Survival and disease-free survival were measured from the time of initial therapy. Kaplan-Meier analyses of survival and remission duration were calculated with 95% confidence intervals twice the SEM. Statistical tests on prognostic variables for remission duration were performed with the Mantel Cox test. Deaths in remission are treated as relapses, and withdrawals are evaluated up to the time of withdrawal from the study. Data are analyzed as of July 1986.

RESULTS

Patients. The 81 patients ranged in age from 16 to 48 years (median age 24 years) (Table 3). There were 47 male and 34 female patients. No patients were excluded because of their clinical condition.

Included in the study group are several patients with "unfavorable prognostic features," including 7 patients with initial CNS involvement, 14 with mediastinal masses, 12 with WBC counts >100,000/μL, and 6 with WBC counts >300,000/μL. The presence of a mediastinal mass was strongly associated with male sex (13 of 14), high WBC count (median 69,000/μL), and T cell phenotype (11 of 13 tested). In contrast, CNS involvement was not associated with these features; all seven patients had WBC counts <50,000/μL, and only one had the T cell phenotype.

All patients had the diagnosis of ALL confirmed by the presence of at least one immunologic lymphoid marker. Seventy-two of 75 patients (96%) tested were positive for TdT (Table 4). One TdT-negative patient strongly expressed BA-1, and two patients expressed numerous T cell antigens, including Leu 1 and Leu 9. Sixty-four patients (79% of the study group) were extensively immunophenotyped using monoclonal antibodies. Forty of these 63% were CALLA-positive. Three of these patients had anomalous expression of Leu 5 with no expression of the pan-T antigens Leu 1 or Leu 9. These three patients strongly expressed B cell markers (BA-1 or Leu 12) and are classified as B lineage, CALLA-positive. Four other patients expressed B lineage markers (BA-1 or Leu 12) but were CALLA-negative. Five patients are considered to have "null" cell ALL based on the absence of CALLA, B, or T lineage markers. Fifteen patients had T

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Patients entered</td>
<td>81</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>16-48 (median 24)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>47 (58%)</td>
</tr>
<tr>
<td>F</td>
<td>34 (42%)</td>
</tr>
<tr>
<td>BC count (10³/μL)</td>
<td></td>
</tr>
<tr>
<td>&lt;20,000</td>
<td>47</td>
</tr>
<tr>
<td>&gt;20,000</td>
<td>34</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>12</td>
</tr>
<tr>
<td>&gt;300,000</td>
<td>6</td>
</tr>
<tr>
<td>Medial mass</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>CNS disease</td>
<td>7 (9%)</td>
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</tbody>
</table>

CNS, central nervous system.

Table 2. Consolidation Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Days</th>
</tr>
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<tbody>
<tr>
<td>Treatment A (cycles 1,3,5,7)</td>
<td>Daunorubicin 50 mg/m² IV, days 1,2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vincristine 2 mg IV, days 1,8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisone 60 mg/m² PO, days 1-14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-Asparaginase 12,000 U/m³ IM days 2,4,7,9,11,14</td>
<td></td>
</tr>
<tr>
<td>Treatment B (cycles 2,4,6,8)</td>
<td>Teniposide 165 mg/m² IV, days 1,4,8,11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside 300 mg/m² IV, days 1,4,8,11</td>
<td></td>
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<tr>
<td>Treatment C (cycle 9)</td>
<td>Methotrexate 690 mg/m² IV, over 42 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leucovorin 15 mg/m² every 6 h x 12 doses beginning at 42 hours</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
cell ALL, based on the presence of Leu 1 or Leu 9. Thirteen were E rosette positive (either by rosette assay or presence of Leu 5), and one of these patients was also CALLA-positive. The E rosette-negative T cell patients expressed Leu 1 and Leu 9, respectively. Two of 20 patients tested expressed the myeloid antigens My7 or My9.

**Induction of remission.** Seventy-six of 81 patients (94%) achieved complete remission. Only one patient failed to achieve hematologic remission. This patient had progressive disease during the second week of chemotherapy and was taken off study. One patient died of asparaginase hepatotoxicity. Three other patients achieved hematologic remission but had persistent systemic candidiasis that precluded their receiving further chemotherapy; they were therefore considered induction failures. Of 76 patients in remission, 41 received 3 doses of daunorubicin, 31 required 4 doses of daunorubicin, and 4 patients had therapy extended to 6 weeks before achieving complete remission.

**Duration of remission and survival.** Kaplan-Meier analysis projects that 53% ± 9% (SEM) of patients achieving complete remission will remain in continuous complete remission at 3 years (Fig 1). Kaplan-Meier analysis projects that 64% ± 9% (SEM) of all patients will be alive at 3 years (Fig 2). Disease-free survival for all patients entered on study is projected to be 50% ± 9% (SEM) at 3 years (Fig 3).

Of 76 patients in complete remission, 15 have been withdrawn from study, 3 have died in complete remission, and 18 have relapsed (Table 5). Forty patients remain in continuous complete remission (CCR) from 3 to 52 months, with median follow-up of 16 months. Twenty-seven patients have been in remission >1 year, 17 patients have been in remission 2 years, and 8 patients remain in remission >3 years.

Fifteen patients were withdrawn from study. These patients did not have a high incidence of unfavorable prognostic features and were not selected for alternative therapy because of an anticipated poor outcome. Six were treated with bone marrow transplantation, 1 developed anaphylaxis to the initial dose of VM-26, 5 moved or were lost to follow-up, and 3 were withdrawn because of major protocol violations. Two of these violations occurred because the patient refused further therapy; one violation occurred because the physician refused to administer scheduled therapy (despite adequate peripheral blood counts) because of marked bone marrow hypocellularity.

There have been 18 relapses between 1 and 51 months of complete remission. Seventeen relapses occurred in bone marrow. One relapse (in a patient with CNS disease at initial diagnosis) occurred simultaneously in the bone marrow and CNS. Most relapses occurred early, and only three patients relapsed after 19 months. The late relapse at 51 months developed in a patient with transfusion-related AIDS.

Factors that may have influenced remission duration were analyzed (Table 6). Neither age, sex, WBC count, presence of CNS disease, number of doses of daunorubicin required to induce remission, nor immunologic subtype had a significant effect on remission duration (Fig 4).
Toxicity. During remission-induction therapy, all patients had reversible alopecia. Nausea and vomiting were minimal, and stomatitis did not occur. Peripheral neuropathy related to vincristine was usually mild and was significant only in the small group of patients who received 6 weeks of induction chemotherapy.

Side effects related to L-asparaginase were common but were rarely threatening. One patient died during induction therapy of asparaginase hepatotoxicity. One patient developed severe hypersensitivity to the initial dose of Escherichia coli asparaginase and was treated with Erwinia asparaginase without problems. One patient developed symptomatic pancreatitis. One patient developed severe hepatic and renal toxicity attributed to asparaginase after 7 doses and another received only 10 of 12 planned doses because of progressive lethargy. Subclavian thromboses at the site of the Hickman catheter occurred in three patients. Abnormalities of glucose tolerance and liver function were common but were not considered an indication to discontinue the drug.

Hematologic toxicity of remission-induction therapy was within the expected range. Thrombocytopenia developed in most patients, and 70% required platelet transfusions. The platelets recovered to >100,000/µL at a median of 18 days. Neutropenia developed in all patients, and 62% were treated with prophylactic low-dose trimethoprim-sulfamethoxasole. There were no infection-related deaths, but three patients failed to respond adequately to amphotericin treatment of systemic candidiasis and could not receive planned consolidation chemotherapy. The median duration of hospitalization for patients during remission-induction was 28 days.

Central nervous system prophylaxis with cranial radiation and intrathecal methotrexate was generally well tolerated. Symptoms of arachnoiditis with headache, nausea, and vomiting developed in 20% of patients, and delayed toxicity of cranial radiation (somnolence syndrome) occurred in 10% of patients.

Consolidation therapy with daunorubicin, vincristine, prednisone, and asparaginase was complicated by fever requiring antibiotics in 10% (21 of 219) of courses. Patients often developed profound neutropenia (<100/µL), but the duration of severe neutropenia was brief. The median length of these cycles of therapy until the next chemotherapy was 33 days. Several complications of L-asparaginase treatment occurred during these consolidation cycles. One patient developed severe hemorrhagic pancreatitis. She recovered from this episode but died during her next chemotherapy course of noninfectious respiratory failure associated with numerous pancreatic pseudocysts. One patient developed severe hypersensitivity and was subsequently treated with Erwinia asparaginase without adverse events. One patient developed massive femoral and iliac venous thrombosis and was successfully treated with streptokinase and heparin. Three patients developed clinical evidence of cardiomyopathy. One had inadvertently received three doses of doxorubicin (50 mg/m²) during induction chemotherapy and had subsequently received a cumulative dose of 400 mg/m² of daunorubicin during consolidation therapy. Two others had received cumulative doses of 600 mg/m² of daunorubicin.

Consolidation therapy with VM-26 plus Ara-C was complicated by fever and neutropenia requiring systemic antibi-

![Figure 4](http://www.bloodjournal.org)  
**Fig 4.** Kaplan-Meier analysis of remission duration by immunophenotype. Tick marks: patients continuing in remission.
In our treatment group are several conditions, since profound neutropenia developed in most patients and usually lasted 7 to 10 days. Infections were most commonly caused by enteric gram-negative organisms, but several patients developed _Candida_ esophagitis and one patient developed disseminated candidiasis. There were 2 treatment-related deaths, 1 due to noninfectious respiratory failure associated with pancreatic pseudocysts, and 1 due to marantic endocarditis superimposed on underlying rheumatic valvular disease.

The final consolidation therapy treatment with methotrexate was well tolerated. Mild mucositis occurred infrequently, and there was no significant hematologic toxicity. Oral maintenance therapy was generally well tolerated. However, the majority of the patients received 75% of the planned dose because of hematologic toxicity, and one patient with cardiomyopathy died of infection.

Median hospitalization time during the entirety of post-remission-induction therapy was 19 days. Four of these days were required for administration of the methotrexate infusion, and 15 days were required for antibiotic treatment of episodes of fever and neutropenia. Patients thus spent a median of 47 days in the hospital during the entire period of treatment.

**DISCUSSION**

The question of the criteria for the diagnosis of adult ALL is a difficult one. The results of the treatment program may be critically dependent on the population studied. The diagnosis of ALL is not as straightforward in adults as it is in children, since the typical L1 morphology is apparent in only 20% to 30% of cases. We used available diagnostic techniques to define our ALL population as accurately as possible. We required not only that cells fail to exhibit myeloid characteristics by histochemical stains, but also that the cells be positively identified as lymphoid by an immunologic technique. This was done in an attempt to exclude occult cases of acute myeloid leukemia that would exhibit peroxidase positivity only at an ultrastructural level.

Our patient group is representative of most groups of adult ALL. No patients were excluded because of their clinical condition. Included in our treatment group are several patients traditionally defined as having poor prognostic features. Seven patients initially had CNS involvement, 12 patients had WBC counts >100,000/µL, and 6 patients had extreme hyperleucocytosis with WBC counts >300,000/µL. Seventy-nine percent of patients were extensively immunophenotyped using monoclonal antibodies. The most common reason for failure to phenotype was inapplicable bone marrow with low circulating blast counts. We were able to phenotype some of these patients, however, using in vitro antibody binding to biopsies placed in saline. The distribution of immunologic subtypes of ALL in our study is similar to that in other reported series (Table 4). Sixty-three percent of patients studied were classified as “common” ALL, and 23% had T cell disease.

The goal of our induction chemotherapy was to achieve normal bone marrow function (complete remission) as quickly as possible without undue toxicity. The importance of avoiding toxicity is highlighted by the fact that, in the past, more induction failures had been due to therapy-related complications than to chemotherapy-resistant disease. On the other hand, early studies at St Jude’s Hospital suggested that the results of the early phases of treatment were critical in determining overall outcome and that more intensive subsequent treatment may not be able to overcome poor initial cytoreduction. Recently, the importance of intensive induction chemotherapy was demonstrated by two groups treating childhood ALL. In one prospective randomized clinical study of childhood ALL, the addition of an anthracycline to the remission-induction program improved long-term disease-free survival from 39% to 64%.

At a minimum, an optimal remission-induction program for adult ALL should include an anthracycline in addition to vincristine and prednisone. The Cancer and Leukemia Group B recently demonstrated in a randomized prospective study that adding daunorubicin to vincristine and prednisone increased the remission rate from 47% to 78%. Although the period of neutropenia was increased by the addition of daunorubicin, no increase in either severe or fatal infections occurred in the more intensively treated group. One may actually be able to reduce overall toxicity by achieving complete remission more rapidly, thereby avoiding prolonged pancytopenia caused by the sequential addition of increments of therapy. Several other recent studies showed that the combination of daunorubicin, vincristine, and prednisone consistently produced a complete remission of ~80% in adult ALL.

Given the complete remission rate of 80% using daunorubicin, vincristine, and prednisone, and the relatively small number of patients with adult ALL available for study, one cannot demonstrate a remission-induction advantage to the addition of asparaginase to this program. Asparaginase can, however, be a useful agent for remission induction, and the best reported results for remission induction in children with relapsed ALL have been produced by four-drug regimens that included asparaginase.

Our remission-induction program has been very successful, with 94% of patients entering complete remission. The toxicity of the program was not severe, and profound neutropenia usually lasted only several days. Systemic antibiotics were needed in only 62% of patients, and life-threatening infections were not common. Patients were generally in excellent clinical condition at the completion of induction therapy and could proceed directly to consolidation therapy without delay.

One novel aspect of our treatment program was the repeated use of VM-26 and Ara-C in consolidation therapy. It was the early experience with this synergistic combination that prompted the design of this study. In early studies, VM-26 produced a low response rate when used as a single agent. Increasing the dose and adding vincristine and prednisone produced a 30% remission rate in children with relapsed ALL, however. VM-26 given in combination with Ara-C, produced exciting results. In one study, 3 of 4 patients who failed to respond to initial intensive induction therapy entered complete remission, and 2 of these patients remained in remission 30 months later when they completed therapy. To have produced this disease-free survival in patients with a
dismal prognosis was unprecedented, and suggested that this combination would be a major addition to our therapeutic armamentarium. Further studies suggested a beneficial role for VM-26 plus Ara-C as consolidation therapy for ALL. One report demonstrated that the addition of a single consolidation course with these agents prolonged remission duration and produced more long-term disease-free survivors.29 This, however, was not confirmed in a second study.30

Repeating courses of VM-26 plus Ara-C have improved the outcome in high-risk pediatric ALL.31

Alternating with cycles of VM-26 plus Ara-C, we treated patients with a four-drug program that included asparaginase in a total dose of 72,000 U/m2. We chose this dose of asparaginase based on dose–response relationships established in pediatric ALL.32 33 Few adult treatment programs have used repeated large doses of L-asparaginase,29 and this represents a second novel aspect of our treatment program. The potential usefulness of asparaginase in consolidation therapy in children has been demonstrated by a randomized study showing longer disease-free survival in asparaginase-treated patients.34

One of the goals of the study was to determine if more effective therapy would change the significance of factors previously reported to be of prognostic importance in adult ALL. We particularly wondered if more effective therapy would diminish the importance of adverse prognostic features. Most reported studies of adult ALL show a strong prognostic significance for WBC count at diagnosis.13, 18, 20, 21, 25 The prognostic significance of immunologic subtype has been variable.13, 18, 20, 21, 36 At this point in our analysis, neither age, sex, WBC count, nor immunologic subtype has prognostic significance with respect to either remission induction or remission duration. Our assessment of prognostic factors differs from those of previous studies. Because many of our patients are still at risk for relapse, however, it is too early to draw firm conclusions from this analysis.

Intensified chemotherapy has been convincingly shown to improve the outcome in high-risk pediatric ALL.37 Our treatment results are very encouraging and add to the increasing evidence that intensive treatment has improved the long-term outcome of adult ALL as well. During the 1970s, only 15% of adult ALL patients remained disease-free at 5 years. The L10 protocol at Memorial Hospital now has a large enough patient group and long enough follow-up to be confident that results of treatment have indeed improved.13, 18 Thirty-five percent to 40% of all patients entered are projected to remain disease-free at 5 years, and most are probably being cured of their disease.

In conclusion, we have developed an intensive treatment program for adult ALL that has been successful in improving disease-free survival. Although our treatment program is prolonged, the intensive phase is completed in 11 months and subsequent oral maintenance therapy is very well tolerated. The program was carried out at several different institutions as well as by private physicians and was relatively easy to administer. Patients spent <7 weeks in the hospital during all therapy. Although longer follow-up will be necessary to determine the ultimate impact of this program, we are hopeful that a substantial fraction of patients will be cured of their disease.

REFERENCES


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