Treatment of Adult Acute Lymphoblastic Leukemia with Intensive Cyclical Chemotherapy: A Follow-up Report

By Charles A. Linker, Lee J. Levitt, Margaret O'Donnell, Stephen J. Forman, and Curt A. Ries

We treated 109 patients with adult acute lymphoblastic leukemia (ALL) diagnosed by histochemical and immunologic techniques. Patients were excluded only for age greater than 50 years and Burkitt’s leukemia. Treatment included a four-drug remission induction phase followed by alternating cycles of noncrossresistant chemotherapy and prolonged oral maintenance therapy. Eighty-eight percent of patients entered complete remission. With a median follow-up of 77 months (range, 48 to 111 months), 42% ± 6% (SEM) of patients achieving remission are projected to remain disease-free at 5 years, and disease-free survival for all patients entered on study is 39% ± 5%. Failure to achieve remission within the first 4 weeks of therapy and the presence of the Philadelphia chromosome are associated with a 100% risk of relapse. Remission patients with neither of these adverse features have a 48% ± 6% probability of remaining in continuous remission for 5 years. Patients with T-cell phenotype have a favorable prognosis with 59% ± 13% of patients achieving remission remaining disease-free compared with 31% ± 7% of CALLA-positive patients. Intensive chemotherapy may produce prolonged disease-free survival in a sizable fraction of adults with ALL. Improved therapy is needed, especially for patients with adverse prognostic features.

During the past decade, the use of intensive chemotherapy regimens has led to considerable improvement in the prognosis of adult acute lymphoblastic leukemia (ALL). Several studies with large numbers of patients and extended follow-up have shown that approximately one-third of such patients can be cured with currently available therapy.1,2 Based on the analysis of prognostic factors, subgroups of patients achieving initial remission have been identified that have a greater than 50% probability of remaining continuously disease-free.3,4 Intensive therapy has also benefited children with high-risk ALL, and their prognosis is similar to that of standard-risk children treated with less intensive regimens.5

We designed a treatment program using intensive, cyclical chemotherapy and have previously reported the preliminary results.6 We used a four-drug remission induction phase to achieve early cytoreduction. After delivering prophylactic treatment to the central nervous system (CNS), we administered repeated courses of intensive systemic chemotherapy using alternating courses of noncrossresistant drugs. One of these combinations included substantial doses of L-asparaginase, an agent previously used primarily in the pediatric age range. This combination alternated with the synergistic combination of teniposide (VM-26) and cytosine arabinoside (Ara-C). We initially reported a high remission rate (94%) and, with a median follow-up of 16 months, projected a continuous complete remission (CCR) rate of 53% at 3 years. We now report more mature data using this same treatment with a larger number of patients and median follow-up over 6 years. We confirm the ability to achieve a high rate of CR (88%) and project that 42% ± 6% (SEM) of patients achieving initial remission will remain continuously disease-free.

Materials and Methods

Patients. One hundred nine consecutive adults with ALL aged less than 50 years who were seen either at the University of California, 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 May 1987. Patients were either previously untreated, or had received less than 2 weeks of therapy with vincristine and prednisone.

Patients were diagnosed as having ALL if morphology was compatible with that diagnosis and if histochemical stains for both peroxidase and α-naphthyl butyrate esterase were negative. In addition, at least one positive lymphoid marker had to be present. The marker used to establish lymphoid lineage was terminal deoxynucleotidyl transferase (TdT) in 101 patients, common ALL antigen (CD10) in four patients, T-cell antigens Leu-1 and Leu-9 (CD5, CD7) in three patients, and B-cell antigen BA1 (CD24) in one patient. Immunophenotyping was performed by indirect immunofluorescence using previously described methods.6 All patients had greater than 50% blasts in the bone marrow (BM), and patients with lymphoblastic lymphoma alone were not included. Patients were excluded only because of age greater than 50 years or mature B-cell (Burkitt’s) leukemia. CNS disease was defined as the presence of any lymphoblasts in the cerebrospinal fluid.

Treatment. All patients gave informed consent according to guidelines approved by each institution’s Committee on Human Research. Chemotherapy was administered as previously reported.6 Remission was induced with daunorubicin, vincristine, prednisone, and asparaginase (Table 1). Patients not in remission at 4 weeks had induction therapy extended for an additional 2 weeks. Patients not entering CR after 6 weeks of induction therapy were considered treatment failures and were taken off study.

CNS prophylaxis was initiated within 1 week of the achievement of CR. Eighteen hundred rads of cranial radiation were delivered in 10 fractions over 12 to 14 days. Six weekly doses of 12 mg of intrathecal methotrexate were administered concurrently by lumbar puncture. 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 the first year of therapy and their dose of cranial radiation was increased to 2,800 rads.

Courses one, three, five, and seven of consolidation chemotherapy were considered treatment failures and were taken off study.

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Table 1. Remission Induction Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Administration</th>
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<tbody>
<tr>
<td>Daunorubicin</td>
<td>50 mg/m² IV, days 1-3</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg IV, days 1, 8, 15 and 22</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² PO, days 1-28</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>6,000 U/m² IM, days 17-28</td>
</tr>
</tbody>
</table>

If BM on day 14 has residual leukemia:
- Daunorubicin: 50 mg/m², day 15

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

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

Table 2. Consolidation Therapy

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

The 109 patients ranged in age from 16 to 49, with a median age of 25. The white blood cell (WBC) count ranged from 0.2 to 960 × 10⁶/μL with a median of 14,000/μL. Sixty-four percent of patients were male. Thirty-three percent of patients were Hispanic, and 40% were either Hispanic, Asian, or Black.

No patients were excluded because of their clinical condition, and three patients who died during induction chemotherapy were severely ill at the time of admission. Patients with unfavorable prognostic features are included in the study group. Seven patients (6%) had CNS disease, 16% had WBC counts greater than 100,000/μL, and 11% had more extreme hyperleukocytosis with WBC counts in excess of 200,000/μL.

Nineteen patients presented with a mediastinal mass on chest x-ray. The presence of a mediastinal mass was correlated with male sex (16 of 19) and T-cell phenotype (13 of 18 tested). The median WBC count was 69,000/μL (compared with 9,000/μL in those without mediastinal mass), and 7 of 19 patients had WBC counts greater than 100,000/μL. No patient in this group had the Philadelphia (Ph) chromosome.

Seven patients presented with CNS disease at diagnosis. In contrast to mediastinal mass, this finding was not correlated with any other clinical feature. The median WBC count for these patients was 13,000/μL, and only one patient had a WBC count greater than 50,000/μL. Only one of seven tested patients had the T-cell phenotype, and five of seven tested were CALLA-positive. No patients had the Ph chromosome.

All patients had the diagnosis of ALL confirmed by the presence of at least one immunologic marker. One hundred one of 104 patients tested (97%) were positive for TdT. One of the TdT-negative patients had early B-lineage disease with expression of BA1 and Leu-12, but absent CALLA. Two patients had T-cell phenotype with expression of Leu-1 and Leu-9.

Ninety-one patients (83% of the group) were extensively immunophenotyped using a panel of monoclonal antibodies. Sixty patients had the phenotype of “common ALL,” based on expression of the common ALL antigen (CD10). Four patients had anomalous expression of Leu-5 without coexpression of Leu-1 or Leu-9. Four of 22 CD10-positive patients tested expressed myeloid antigens My7 (CD13) or My9 (CD33), and eight of 33 patients tested had the Ph chromosome, including one of the four patients who expressed myeloid antigens.

Four patients had early B-lineage disease based on expression of BA1 or Leu-12 without concomitant expression of CALLA. One of these patients had anomalous expression of Leu-5 without other T-cell antigens. Two patients were tested for myeloid antigens and no expression was found. All four patients had adequate cytogenetic evaluation. None expressed the Ph chromosome and one had t(4,11).

Nineteen patients had T-cell disease defined by expression of Leu-1, Leu-9, or the presence of sheep erythrocyte rosetting in the absence of B-lineage markers. All 16
patients tested for Leu-9 were positive, as were 13 of 16 patients tested for Leu-1. Sixteen of 18 patients tested expressed Leu-5. One of eight patients tested coexpressed myeloid antigens and one patient (with strong expression of Leu 1, 5, and 9) coexpressed CALLA. Eight patients underwent adequate cytogenetic evaluation. None of these eight patients expressed the Ph chromosome. One patient had t(1,7) with the break point on chromosome 7 involving the β-chain of the T-antigen receptor.

Eight patients had null cell disease defined by the finding of a positive TdT and the absence of T- or B-lineage markers. All seven patients tested strongly expressed HL A-Dr. No patients were tested for myeloid antigen expression. Five patients underwent cytogenetic evaluation; two had the Ph chromosome and one had trisomy 8. Based on response to therapy, this patient with trisomy 8 likely had nonlymphocytic leukemia.

Expression of myeloid antigens My7 or My9 was examined in 32 patients, and five (16%) were positive. The five positive cases included four with common ALL (one Ph chromosome-positive) and one with T-cell disease and t(1,7).

Fifty-four patients (50% of the group) had adequate cytogenetic evaluation. Thirty-three patients were normal. The Ph chromosome was found in 10 patients, 9% of the entire patient group, but 19% of the patients tested. Additional abnormalities of note included t(4,11) in one patient and hyperdiploidy in three patients. The 10 Ph chromosome-positive patients included eight with common ALL and two with null cell phenotype. There were no distinguishing clinical features of the Ph chromosome-positive group. The median WBC count was 21,000/μL and the median age was 27 years.

Remission induction. CR was achieved in 96 patients (88%) (Table 3). Seven patients failed to respond to chemotherapy and six failed because of toxicity (four deaths during induction and two persistent medical problems preventing consolidation therapy). The chemotherapy nonresponders were characterized by recognized adverse prognostic features. The median WBC count in this group was 98,000/μL as opposed to 12,000/μL in the chemotherapy responders. Three of the seven nonresponders were Ph chromosome-positive. The Ph chromosome-negative nonresponders included one with null cell phenotype and trisomy 8, one with common ALL and a WBC count of 98,000/μL, and one with a T/myeloid phenotype and a WBC count of 540,000/μL. Only one chemotherapy failure had no identifiable risk factor, and this patient was not evaluated with cytogenetics.

The six patients who failed to enter CR because of toxicity were characterized by older age (median 40 vs 24 years in the chemotherapy responders). Deaths were caused by enterocolitis with overwhelming sepsis in two patients, aspergillus pneumonia in one patient, and asparaginase hepatotoxicity in one patient. Two patients entered hematologic remission but were unable to receive consolidation therapy because of persistent visceral candidiasis; these patients were considered to have failed induction therapy due to toxicity.

Of the 109 patients treated, two developed progressive disease before day 14 and were considered early chemotherapy failures. Fifty-three of 107 patients examined had no residual leukemia on the day 14 BM examination, and received only the three initial doses of daunorubicin. Forty-eight of these 53 patients achieved CR, and five failed because of toxicity. Fifty-four patients had residual leukemia on the day 14 BM and received a fourth dose of daunorubicin. Forty-one of these patients achieved remission by day 28, two developed progressive disease, and one died of toxicity. Ten patients had residual leukemia on the day 28 BM and received six total doses of daunorubicin. Of these 10, seven achieved CR and three failed to respond to chemotherapy. Overall, 89 patients (82%) achieved CR within 4 weeks.

Induction chemotherapy was generally well tolerated. Systemic antibiotics other than prophylactic trimethoprim/sulfamethoxazole were required in 63% of courses, and platelet transfusions were administered in 67% of courses. Patients were discharged from the hospital at a median of 28 days from initiation of therapy. Neutrophils recovered to greater than 1,000/μL at a median of 23 days from initiation of therapy and profound neutropenia was of brief duration. Platelets recovered to greater than 100,000/μL at a median of 18 days from initiation of therapy. Addition of a fourth dose of daunorubicin based on the day 14 BM had no effect on platelet recovery or time to hospital discharge, but did prolong recovery to 1,000 neutrophils from a median of 20 to 27 days.

Nonhematologic toxicity was generally mild. All patients developed reversible severe alopecia. Nausea and vomiting were minimal and significant stomatitis did not occur. Peripheral neuropathy related to vincristine was usually mild and was significant only in the group of patients who received 6 weeks of induction therapy.

Side effects related to L-asparaginase were common but were usually not life-threatening. One patient died of asparaginase hepatotoxicity. One patient developed severe hypersensitivity and completed therapy with Erwinia asparaginase without difficulty. Several patients received fewer than the 12 planned doses of asparaginase because of generalized malaise or progressive abnormalities in liver function. Three patients developed subclavian thromboses at the site of Hickman catheter.

CNS prophylaxis. Cranial irradiation and intrathecal methotrexate commonly caused malaise and lethargy, but not significant toxicity. Symptoms of arachnoiditis with

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<th>Table 3. Results of Therapy</th>
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<tr>
<td>Patients entered</td>
</tr>
<tr>
<td>Induction failure</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Withdrawal</td>
</tr>
<tr>
<td>Receive consolidation therapy</td>
</tr>
<tr>
<td>Relapse</td>
</tr>
<tr>
<td>Death in remission</td>
</tr>
<tr>
<td>Unrelated death</td>
</tr>
<tr>
<td>CCR</td>
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headache, nausea, and vomiting developed in 20% of patients, and delayed toxicity of cranial irradiation (somnolence syndrome) occurred in 10% of patients.

Consolidation therapy. Consolidation therapy with daunorubicin, vincristine, prednisone, and asparaginase was complicated by fever requiring antibiotics in 9% (28 of 295) of courses. Myelosuppression was usually profound but short-lived and patients began their next cycle of chemotherapy at a median of 32 days from start of therapy. There were no treatment-related deaths during these courses, but one patient developed severe hemorrhagic pancreatitis that was a major contributing factor in her death during a subsequent consolidation course, and a second patient developed hemorrhagic pancreatitis requiring draining of a pseudocyst. One patient developed hypersensitivity to Escherichia coli asparaginase during consolidation but successfully completed therapy with Erwinia asparaginase. An additional patient receiving asparaginase developed massive lower extremity deep venous thrombosis requiring streptokinase in addition to heparin to successfully resolve. Clinically evident cardiomyopathy developed in three of 59 patients completing four courses of anthracycline-based chemotherapy with cumulative daunorubicin doses of 550 to 600 mg/m².

Consolidation therapy with VM-26 plus Ara-C was complicated by fever and neutropenia requiring systemic antibiotics in 37% (101 of 273) of courses. Myelosuppression was considerable and patients began their subsequent cycles of chemotherapy at a median of 40 days from initiation of these cycles. There were three treatment-related deaths due to overwhelming sepsis, marantic endocarditis, and respiratory failure superimposed on pancreatic pseudocyst resulting from prior asparaginase-related pancreatitis. Two patients were withdrawn from therapy because of anaphylaxis to VM-26.

The final consolidation therapy with moderate-dose methotrexate was well tolerated. There was no significant hematologic toxicity and only minimal mucositis. Oral maintenance therapy was generally very well tolerated. However, the majority of patients required dose reduction because of hematologic toxicity. One patient with anthracycline-related cardiomyopathy died of infection during oral maintenance therapy.

Overall, patients were hospitalized for a median of 25 days during consolidation therapy, 21 because of complications, and 4 to receive the moderate-dose methotrexate infusion. Thus, patients spent a median of 53 days in the hospital during the entire period of treatment.

Results of therapy. With a median follow-up of 77 months (range, 48 to 111), Kaplan-Meier analysis projects that 42% ± 6% (SEM) of patients achieving CR will remain in CCR (Fig 1). For all 109 patients entered on study, actuarial survival is 40% ± 5% and DFS is 35% ± 5% (Fig 2).

Of 96 patients in remission, 77 proceeded to consolidation therapy and 19 patients were withdrawn from study (Table 4). Two factors predicted for dismal outcome with all patients relapsing within 3 years. All patients with the Ph chromosome relapsed (Fig 3, P = .007) as did all patients who required 6 weeks of induction chemotherapy to enter remission (Fig 4, P = .02). For patients who are Ph chromosome-negative and enter remission within 4 weeks of therapy, the projected CCR rate is 48% ± 6% at 5 years (Fig 5).

Immunophenotype appears to have an influence on institution (City of Hope) as part of a study to determine the role of BMT in the treatment of ALL during first CR. Patients were not withdrawn for BMT on the basis of adverse prognostic features, but rather based on availability of a suitable donor. (Currently, six of eight patients are alive and in CR from 1,456 to 2,863 days after BMT. Two patients relapsed at day +93 and day +314.) Five patients refused further therapy. In two of these patients, refusal could be attributed to toxicity during induction chemotherapy. In three others, refusal was due to psychiatric illness. Three other patients moved out of the country and were lost to follow-up. Two patients were withdrawn because of anaphylaxis to VM-26, and one patient (who remains in prolonged remission) was deemed ineligible because of major protocol violations. Four patients died of treatment-related complications and there was one unrelated death. Forty-three patients relapsed, 41 in BM, one in BM and CNS, and one in the testis.

Factors influencing remission duration (for patients achieving remission) were analyzed (Table 4). Two factors predicted for dismal outcome with all patients relapsing within 3 years. All patients with the Ph chromosome relapsed (Fig 3, P = .007) as did all patients who required 6 weeks of induction chemotherapy to enter remission (Fig 4, P = .02). For patients who are Ph chromosome-negative and enter remission within 4 weeks of therapy, the projected CCR rate is 48% ± 6% at 5 years (Fig 5).

Immunophenotype appears to have an influence on
Table 4. Prognostic Variables for Remission Duration

<table>
<thead>
<tr>
<th></th>
<th>No. Achieving Remission</th>
<th>No. Receiving Consolidation</th>
<th>5-yr CCR (%)</th>
<th>±(SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CR patients</td>
<td>96</td>
<td>77</td>
<td>42 ±2</td>
<td></td>
</tr>
<tr>
<td>Ph chromosome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>89</td>
<td>73</td>
<td>45 ±6</td>
<td>(P = .007)</td>
</tr>
<tr>
<td>Weeks to achieve CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>71</td>
<td>46 ±6</td>
<td>(P = .02)</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Phenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALLA</td>
<td>52</td>
<td>44</td>
<td>31 ±7</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>18</td>
<td>15</td>
<td>59 ±13</td>
<td>(P = .17)</td>
</tr>
<tr>
<td>Early B</td>
<td>4</td>
<td>4</td>
<td>50 ±25</td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>5</td>
<td>5</td>
<td>40 ±22</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>85</td>
<td>67</td>
<td>44 ±6</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>11</td>
<td>10</td>
<td>26 ±16</td>
<td>(P = .17)</td>
</tr>
</tbody>
</table>

prognosis, although given the sample size, the results are not statistically significant (P = .17). Patients with T-cell phenotype appear to do well with a projected CCR rate of 59% ± 13% (Fig 6). The relapse pattern for T-cell patients appears different from the group as a whole in that all but one relapse occurred within 19 months. The one late relapse (at 33 months) was a case of secondary acute myeloid leukemia. Within the T-cell group, high WBC count did not have a significant impact on outcome, with projected remission rates of 64% and 55%, respectively, for patients with WBC count less than or greater than 100,000/μL. However, all T-cell patients with WBC counts greater than 100,000/μL who relapsed did so within 7 months. Patients with CALLA-positive ALL did less well overall and the relapse pattern appears different. Only 31% ± 7% of patients with CALLA-positive disease are projected to remain disease-free long-term. Unlike patients with T-cell disease, there appears to be a continuous pattern of relapse in the third and fourth year and a plateau is not reached until after the end of the fourth year. Some of the poor outcome of the CALLA-positive group may be attributed to other factors, such as the presence of the Ph chromosome or delayed time to achieving remission. These adverse factors were found in eight of 30 relapses. Elevated WBC count is a poor prognostic factor within the CALLA-positive subgroup, and all patients with WBC counts greater than 100,000/μL relapsed quickly (P = .001). Patients with CALLA-positive ALL without any of these three risk factors have a CCR rate of 39% ± 9%.

Given that the patient population is limited to adults less than 50 years old, age was not a significant adverse factor in our study. However, there is a trend for patients greater than 40 years of age doing less well with a projected CCR rate of 28% ± 16% as opposed to 44% ± 6% in younger patients (P = .17). Neither sex, WBC count, presence of CNS disease, nor requirement for a fourth dose of daunorubicin on day 14 of induction were predictive of outcome. Patients with no leukemia on day 14 of induction (receiving three doses of daunorubicin) have a projected CCR rate of 51% ± 8% compared with 40% ± 8% for patients achieving remission after four doses of daunorubicin.

**DISCUSSION**

Long-term follow-up confirms our initial observations that intensive chemotherapy can produce a very high rate of CR for adults with ALL, and that more than 40% of these patients who achieve remission will have prolonged DFS. We have observed no relapses after 5 years of CCR and are...
The group of patients we treated are very similar in most respects to groups of adult ALL patients reported in other series. Our patients were unsel ected except for age less than 50 years and Burkitt’s leukemia, and included patients who were seriously ill at diagnosis or had ominous prognostic features. Forty percent of our patients were either Hispanic or non-Caucasian, a proportion that may be higher than seen in other American or European studies. Black race has been reported to be an adverse prognostic feature in childhood ALL,
but whether it has impact in adult disease remains to be determined. The patients were treated in several institutions, including three large centers, and 31% of the group were treated in community settings.

The patient group was well defined immunologically to accurately diagnose ALL and exclude patients with undifferentiated myeloid leukemias. Eighty-three percent of the patients were well characterized immunologically and 50% were characterized with cytogenetic evaluation. The lower rate of cytogenetic evaluation reflects the broad range of institutions from which patients were recruited, as well as the fact that many patients were seen in the early 1980s, when the importance of cytogenetic evaluation had not yet been fully appreciated.

The question of how to define adult ALL is not straightforward. In addition to morphologic and histochemical criteria, we chose to require demonstration of at least one lymphoid marker, usually TdT, to screen out undifferentiated myeloid leukemias. Myeloid surface antigens have been described in a proportion of patients with both childhood and adult ALL. The finding of anomalous myeloid antigen expression has been reported to be of adverse prognostic significance in adult ALL, but conflicting results have been reported in pediatric studies. However, we feel that demonstration of these antigens cannot be used to define leukemia as myeloid. To do so would drastically change the definition of ALL. Given that very few surface antigens are truly lineage-specific, but can be seen in a wide variety of unexpected cell types, it would be an error to place too much reliance on the demonstration of these antigens.

Examining a larger group of patients that now includes the Ph chromosome-positive group, we have confirmed our earlier report indicating that an intensive four-drug induction chemotherapy program can produce a very high rate of CR in adult ALL. The reasons for failure to achieve remission were evenly divided between chemotherapy failure and toxicity of the regimen. We included as induction failures patients in hematologic remission who had persistent candidiasis that prevented them from receiving planned consolidation therapy in a timely fashion. We believe it is appropriate to include these patients as remission induction failures in addition to those who die during therapy.

Although one goal of our induction program was to achieve substantial cytoreduction rapidly, it is necessary to balance antileukemic efficacy with the need to avoid toxicity. Most investigators have found that induction failure is due either equally or primarily to toxicity rather than to ineffectiveness of chemotherapy. Older adults are more prone to toxic death, as evidenced by consistent findings in three recent studies. In our series, even with an upper age limit of 50 years, patients who failed induction due to toxicity were older, with a median age of 40 years. In general, our induction program was relatively nontoxic. Patients were discharged from the hospital by 28 days and were able to proceed to consolidation therapy within 2 weeks.

Given the high CR rate reported in many recent series, it is hard to define an optimal remission induction regimen. Remission rates of 74% to 85% have been reported, with higher rates (77% to 90%) in younger patients. These successful remission induction programs include an anthracycline in addition to vincristine and prednisone. We chose to administer high doses of daunorubicin (150 mg/m²) early in induction therapy and to add intensive asparaginase treatment. Only 6% of patients were chemotherapy nonresponders, a value similar to the 7% to 13% range reported in other recent series. Our patients achieved remission somewhat earlier, with 82% of patients in remission by 4 weeks as opposed to 60% to 66% in remission by this time in other studies. This difference may be due to the earlier use of higher-dose anthracycline in our studies. Clearing of leukemia by day 14 has recently been shown to be of long-term prognostic significance in pediatric disease, but whether this finding will apply to adults remains to be defined.

Given the already high rate of CR with daunorubicin, vincristine, and prednisone, it is difficult to define the role of asparaginase in improving remission induction therapy. It is clear that asparaginase improves remission induction rate when added as a third drug to vincristine and prednisone, but it is possible that the use of daunorubicin obviates the need for asparaginase. Asparaginase has been shown to play a useful role in consolidation therapy. In one randomized pediatric study, the addition of asparaginase was shown to improve long-term DFS. A recent pediatric trial for both standard-risk and high-risk children that produced very encouraging preliminary results relies heavily on asparaginase, and the investigators attribute their improved results to the use of this drug. Improved salvage...
therapy for children, especially those with prolonged initial remissions, has relied on multidrug therapy that included repeated use of asparaginase.\textsuperscript{20} The optimal dose of asparaginase as part of combination chemotherapy in adults remains to be defined. We chose to use a total dose of 72,000 U/m\textsuperscript{2} for each course based on the definition of optimal dose for asparaginase as a single agent in children.\textsuperscript{21,22} However, asparaginase needs to be used more cautiously in adults because of its increased toxicity in this age group.

The major focus of our treatment program was on the use of intensive alternating courses of consolidation chemotherapy. Many studies now support the increased effectiveness of intensive consolidation therapy in the treatment of both adults and high-risk children with ALL. This benefit is especially evident for adults with T-cell disease. T-cell phenotype has now become a favorable rather than an unfavorable prognostic factor and CCR rates of 55% to 58% have been reported in other large series.\textsuperscript{1,5} A common factor in all these successful consolidation programs is the use of Ara-C, either in combination with cyclophosphamide or teniposide. It is striking that when investigators at Iowa omitted an Ara-C-containing early consolidation phase, their T-cell patients did extremely poorly, whereas their overall results compare favorably with other reported series.\textsuperscript{6} This finding strongly suggests that the omission of an Ara-C-containing consolidation was responsible for the failure to control T-cell disease. Pediatric investigators have also shown the usefulness of Ara-C-containing consolidation in controlling T-cell disease. In one report concerning high-risk children with WBC counts greater than 100,000/\mu L (most of whom had T-cell disease), the addition of teniposide and Ara-C during induction and consolidation therapy produced significant benefit in long-term DFS.\textsuperscript{23}

An unexpected finding in our series was the relatively poor outcome of patients with CALLA-positive disease. The CCR rate for these patients was only 31%, which is somewhat lower than reported rates (34% to 53%) of other investigators.\textsuperscript{1,5,4} The poor prognosis of the CALLA-positive group can be explained in part by the presence of the Ph chromosome, or by the failure to go into remission by 6 weeks. Within the CALLA-positive group we also saw an adverse effect of elevated WBC count, with all patients with WBC counts greater than 100,000/\mu L relapsing quickly ($P = .001$). Hoeﬂer et al also noted the adverse impact of other prognostic features, including elevated WBC count, in their CALLA-positive group.\textsuperscript{1} In his study, CALLA-positive patients with no additional adverse factors had a CCR rate of 57%, as opposed to 20% for those with additional adverse factors.

However, even excluding patients with identifiable risk factors, the remaining CALLA-positive group still did less well, with a CCR rate of only 39%. It is possible that this inferior outcome compared with other studies is treatment-related. Our treatment program differed from others in that methotrexate was used only once and then not until the tenth month of therapy. (Our initial decision to use methotrexate in this fashion was based on the concern of producing leucoencephalopathy with high-dose methotrexate infusions in patients previously exposed to both intrathecal methotrexate and cranial radiation.) Methotrexate may thus play an important role in the control of CALLA-positive ALL, and its importance may be underestimated. Several pediatric studies have generated observations that highlight the importance of this drug. In one report using moderate-dose methotrexate, relapse was significantly more common in those who did not achieve levels of 16 \mu mol/L.\textsuperscript{24} Other pediatric programs relying heavily on moderate- or high-dose methotrexate have produced encouraging results,\textsuperscript{26} as has one adult program.\textsuperscript{27}

In our study, we have defined a group at very high risk of relapse based on two adverse prognostic factors. All patients with the Ph chromosome relapsed. This finding has been confirmed by others.\textsuperscript{5,28-31} The Ph chromosome-positive group is a significant one in adult ALL. In our study, 9% of all patients were documented Ph chromosome-positive, but this represented 19% of patients with cytogenetic evaluation. Similarly, at Memorial Hospital, 9% of all patients but 21% of all patients tested were Ph chromosome-positive. Recent reports using probes for bcr-abl suggest that the proportion of adults with the Ph chromosome may be 30% or higher.\textsuperscript{32}

In our study, patients not in remission by 4 weeks invariably relapsed. This finding has been confirmed by others,\textsuperscript{1,5} although the patient groups are not strictly comparable because the number of patients achieving delayed remission in our study was fairly small (7% of remission patients as opposed to 19% in others). However, there appears to be general agreement that the delayed achievement of remission is one of the most significant adverse prognostic features.

The definition of subgroups of adults with ALL with varying prognoses will be critical in determining optimal therapy. In two large studies, “good-risk” patients have been defined with a greater than 60% likelihood of remaining disease-free long-term.\textsuperscript{35} Patients with T-cell disease, and those with CALLA-positive disease who are young, have low WBC counts, and go into remission quickly fit this category. However, patients with high-risk disease do much worse and some patient groups do not appear to be curable with conventional chemotherapy. Patients with the Ph chromosome or patients who are slow to achieve remission fall into this latter group. Patients with elevated WBC counts (excluding those with T-cell disease) also appear to do worse. These groups of patients are candidates for more intensive therapy, and at the present time allogeneic BMT appears to be the treatment of choice. Older adults also have an inferior prognosis, but are not good candidates either for more intensive chemotherapy or for allogeneic transplantation.

The role of allogeneic BMT in the treatment of adults in first remission of ALL remains to be defined.\textsuperscript{34-42} Previous studies have suggested that between 40% and 60% of patients can become long-term disease-free survivors when transplanted during first CR. Many of these patients were selected based on pretransplant characteristics that predicted a high risk of relapse. Whether this approach would
be more effective in patients with lower-risk disease can only be answered in appropriate trials. Patients with Ph chromosome-positive disease have benefited from allogeneic BMT, and our study would also support the concept of early BMT for these patients as well as those who required a prolonged remission-induction phase.

In conclusion, we have documented that this program of intensive, cyclical chemotherapy produces a high rate of CR for adults with ALL, and that patients in remission without detectable features have a 48% chance of remaining disease-free at 5 years. These results, in combination with results of recently reported large series, show the effectiveness of more intensive chemotherapy in controlling adult ALL. For patients with a favorable prognosis, this type of intensive chemotherapy approach can be recommended, and it is possible that further refinements in therapy may improve results further. However, for patients at high risk of relapse, it is unlikely that modifications of conventional chemotherapy will drastically alter their prognosis, and intensified therapy with either allogeneic or autologous BMT will likely be the best approach.

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