Treatment of Acute Lymphoblastic Leukemia in Adults With Intensive Induction, Consolidation, and Maintenance Chemotherapy

By Khader K. Hussein, Steve Dahlberg, David Head, Caroline C. Waddell, Lyubica Dabich, James K. Weick, Francis Morrison, John H. Saiki, Earl Metz, Saul E. Rivkin, Michael R. Grever, David Boldt, and the Southwest Oncology Group

The Southwest Oncology Group conducted a study of acute lymphoblastic leukemia (ALL) in adults over a 5-year period, testing the utility of the L-10M regimen initially described by the group from Memorial Sloan-Kettering Cancer Center. One hundred sixty-eight eligible patients were treated with this comprehensive combination chemotherapy regimen. One hundred fifteen (68%) achieved complete remission. With the current median follow-up time of 34.5 months, the median durations of remission, relapse-free survival, and overall survival were 22.9, 20.3, and 17.7 months, respectively. Only 35% of the patients over 50 years of age achieved a complete remission. Age was a significant prognostic factor for complete response, survival, relapse-free survival, and remission duration. In addition, a low initial WBC count was found to have a statistically significant association with longer remission duration. Responders between the ages of 20 and 49 years with WBC counts of <15,000 appear to have an exceptionally good prognosis.

The Southwest Oncology Group (SWOG) conducted this study, using a regimen identical to the L-l0M protocol. The following monoclonal-antibody panel was used to analyze all specimens in the central laboratory: anti-common ALL antigen (CALLA) (CD10) (J5, Coulter Immunology, Hialeah, FL); anti-immune response gene-associated antigen (Ia) (I2, Coulter); anti-B cell (CD20) (B1, Coulter); anti-T cell (CD2) (T11, Coulter); and anti-myeloid cell (CD11) (OKMI, Ortho Diagnostic Systems, Inc., Raritan, NJ). When sufficient cells were available, additional monoclonal reagents were used, including the following types: T-cell subset-specific antibodies, antithymocyte reagents, and other B-cell- and myeloid-specific antibodies. Terminal deoxynucleotidyl transferase (TdT) determinations were not performed routinely but were available for many subjects.

The results of the immunologic analyses were used to identify four major subclasses of ALL. These subclasses and the criteria used to assign specimens to each are listed in Table 1.

MATERIALS AND METHODS

Eligibility criteria. Previously untreated patients 15 years of age or older with a diagnosis of ALL were eligible for this study. The diagnosis of ALL was established on the basis of morphologic, cytochemical, and immunologic studies. An absolute infiltration of bone marrow with at least 50% blasts or evidence of progressive disease with ≥30% marrow blasts was required, as were normal serum levels of bilirubin and creatinine.

ALL was morphologically classified into three groups in accordance with the French-American-British (FAB) classification, with slight modification by the SWOG pathology review committee. Chromosomal studies were not routinely performed before therapy. Patients with Philadelphia chromosome-positive ALL were not excluded from this analysis. Informed consent was obtained from all patients before the initiation of therapy.

One hundred eighty-two patients were registered in this study between May 30, 1980 and March 29, 1985. One hundred sixty-eight patients were considered eligible. Fourteen patients were ineligible for the following reasons: acute nonlymphocytic leukemia (seven patients); lymphoblastic lymphoma (three patients); secondary leukemia (one Hodgkin’s disease, one sideroblastic anemia); previous therapy (one patient) and chronic myelogenous leukemia in blast crisis (one patient).

Immunologic cell markers. Studies of cell-surface markers were available for 72 patients. Of these, 44 specimens were analyzed in a SWOG central leukemia typing laboratory established in July 1982. Eighteen specimens were analyzed at local SWOG institutions, and 10 specimens were kindly analyzed by Dr. R.S. Metzger of Durham, NC. In the central leukemia typing laboratory, immunophenotyping was performed by indirect immunofluorescence and flow cytometry. A leukemia cell specimen was considered positive for a specific marker if more than 15% of the cells expressed that marker.

The following monoclonal-antibody panel was used to analyze all specimens in the central laboratory: anti-common ALL antigen (CALLA) (CD10) (J5, Coulter Immunology, Hialeah, FL); anti-immune response gene-associated antigen (Ia) (I2, Coulter); anti-B cell (CD20) (B1, Coulter); anti-T cell (CD2) (T11, Coulter); and anti-myeloid cell (CD11) (OKMI, Ortho Diagnostic Systems, Inc., Raritan, NJ). When sufficient cells were available, additional monoclonal reagents were used, including the following types: T-cell subset-specific antibodies, antithymocyte reagents, and other B-cell- and myeloid-specific antibodies. Terminal deoxynucleotidyl transferase (TdT) determinations were not performed routinely but were available for many subjects.

The results of the immunologic analyses were used to identify four major subclasses of ALL. These subclasses and the criteria used to assign specimens to each are listed in Table 1.

From the University of Oklahoma Health Sciences Center, Oklahoma City; Southwest Oncology Group Biostatistical Center, Seattle; University of Utah Medical Center, Salt Lake City; Baylor College of Medicine, Houston; University of Michigan Medical Center, Ann Arbor; Cleveland Clinic Foundation, Cleveland; the University of Mississippi Medical Center, Jackson; University of New Mexico, Albuquerque; Ohio State University Health Center, Columbus; Puget Sound Oncology Consortium, Seattle; and the University of Texas Health Science Center, San Antonio.

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Treatment regimen. The treatment regimen used in this study was identical to the L-10M regimen used at MSKCC. The induction phase consisted of vincristine 2 mg/m^2 administered intravenously (IV) on days 1, 8, 15, 22, and 29 (each dose not exceeding 4 mg in patients under 60 years of age or 2.5 mg in patients over 60). Prednisone was administered at a dosage of 60 mg/m^2 orally on days 1 through 36 and then tapered over seven days and discontinued. Adriamycin (doxorubicin; Adria Laboratories Inc, Dublin, OH) 20 mg/m^2 was administered on days 17, 18, and 19. CNS prophylaxis with intrathecal methotrexate 6 mg/m^2 was administered on days 3, 5, 15, 17, 34, and 36. An Ommaya reservoir was placed at the time of complete remission (or about day 30) in patients with an initial WBC count of 20,000/μL or more. Cyclophosphamide 600 mg/m^2 and Adriamycin 30 mg/m^2, administered IV on day 36, completed the induction phase.

The consolidation phase consisted of three cycles of cytosine arabinoside and methotrexate alternating with three cycles of cytosine arabinoside at 200 mg/m^2 for five days starting on days 1, 3, 5, 15, 17, 34, and 36. An Ommaya reservoir was placed at the time of complete remission (or about day 30) in patients with an initial WBC count of 20,000/μL or more. Methotrexate was administered during this phase at 6 mg/m^2 and Adriamycin 30 mg/m^2, administered IV on day 36, completed the induction phase.

In the maintenance phase, drugs were administered as follows: vincristine 1.4 mg/m^2 IV on days 50 and 57, prednisone 60 mg/m^2 orally for seven days beginning on day 50, and L-asparaginase 60,000 IU/m^2 IV on days 15, 16, and 17. Six-mercaptopurine 90 mg/m^2 orally on days 36 through 65 and 106 through 134; methotrexate 20 mg/m^2 orally on days 43, 50, 57, 64, 113, 120, 127, and 134; and cytosine arabinoside 150 mg/m^2 IV, each given every 12 hours for six days beginning on days 15, 50, and 85. In addition, patients received vincristine 1.4 mg/m^2 IV on days 50 and 57, prednisone 60 mg/m^2 orally for seven days beginning on day 50, and L-asparaginase 60,000 IU/m^2 IV three times weekly for a total of six doses beginning on day 99, followed by cyclophosphamide 1,200 mg/m^2 IV on day 110. Intrathecal methotrexate was administered during this phase at 6 mg/m^2 on days 15, 17, 57, and 59.

During the maintenance phase, drugs were administered as follows: vincristine 1 mg/m^2 IV on days 1, 8, 78, and 85; prednisone 90 mg/m^2 for seven days beginning on days 1 and 78; Adriamycin 20 mg/m^2 IV on days 15, 16, and 17; 6-mercaptopurine 90 mg/m^2 orally on days 36 through 65 and 106 through 134; methotrexate 20 mg/m^2 orally on days 43, 50, 57, 64, 113, 120, 127, and 134; and cytosine arabinoside 1,000 μg/m^2 IV on days 71 and 147; cyclophosphamide 800 mg/m^2 IV and carmustine (BCNU) 80 mg/m^2 on day 91. Intrathecal methotrexate 6 mg/m^2 was administered on days 36, 38, 106, and 108. This maintenance regimen was cycled every 21 weeks for a total of 36 months.

Statistical methods. Estimation of the probability of survival, relapse-free survival (RFS), and remission duration was made according to the method of Kaplan and Meier. Estimates of the median times were also obtained by this method. Comparisons between patient groups were assessed with the log-rank statistic.

The Cox regression model was used to assess differences in a multivariate setting. All significant values were calculated from two-sided tests. Survival was calculated from the date of patient registration to the date of death or most recent follow-up. RFS and remission were calculated from the date of documented remission to the date of relapse, death, or most recent follow-up. RFS includes both relapse and death without relapse as endpoints. Remission duration censors the patients expiring without relapse. Only patients who achieve a complete response are included in the estimations of RFS and remission duration. Seventeen patients who received a marrow graft were censored at the time of transplant in the survival, RFS, and remission-duration estimates and the corresponding statistics.

RESULTS

Patient characteristics. The 168 eligible patients ranged in age from 15 to 85 years (median age, 28 years). Forty patients (24%) were 50 years of age or older; 115 patients (68%) were men and 53 (32%) were women; 137 were white. Eighty-six patients were febrile at presentation. The initial WBC count ranged from 0.6 × 10^3 to 340 × 10^3/μL (median, 13.2 × 10^3/μL). The platelet count ranged from 0.4 × 10^3 to 1330 × 10^3/μL (median, 57 × 10^3/μL). The median hemoglobin was 9.7 g/dL (range, 4.0 to 17.6 g/dL). One hundred forty patients had adequate morphologic evaluation by the central pathology-review committee. Seventy-eight of these patients were L1, 59 were L2, and three were L3.

Immunologic cell markers. Table 1 shows the distribution of immunologic subclasses in the 72 subjects for whom evaluable surface-marker data were available. Among the four patients classified as myeloid antigen-ALL, three had blast cells that expressed myeloid antigens exclusively; in one, the phenotype was CD10+, TDT+, and CD13+.

There were no differences between patients with or without immunophenotyping analysis with respect to the following parameters: age, sex, percentage of circulating blasts, L1 v L2 morphology, complete remission rate, overall survival, RFS, or remission duration. Among the complete responders, patients who had not had cell-surface-marker studies performed had a significantly longer time from the start of therapy to the time of complete response (P = .02, Kruskal-Wallis test).

As a group, patients in whom immunophenotyping was not performed had significantly lower initial leukocyte counts than did those in whom immunophenotyping was performed (P = .02, Kruskal-Wallis test). This was due to recovery of insufficient lymphoblasts for analysis from the peripheral blood of many patients with low total leukocyte and circulating blast counts.

Treatment results. The overall results of this study are summarized in Table 2. The results are updated through November 5, 1987, with a median follow-up time of 34.5 months.

One hundred sixty-eight patients registered in this study were considered eligible; 164 of them were fully evaluable. Two patients were removed from the study during induction.
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Due to toxicity, and two refused further treatment. These patients (17%) died early in the induction phase, before their patients achieved complete remission (CR). Twenty-nine patients are included in this analysis.

The overall remission duration estimates are depicted in Fig 1. The median duration of CR for all responders is 22.9 months. Patients 20 to 49 years of age had significantly longer remission durations than either the younger or older patient groups, as shown in Fig 2 (P < .001). A low initial WBC count (<15,000/μL) was also statistically associated with longer remission duration (P < .04). Using a Cox regression model to examine for both factors simultaneously, we found that both age (<P < .001) and WBC count (<P < .01) remained significantly associated with remission duration. A higher remission duration was observed for patients aged 20 to 49 with low initial WBC counts. This interaction, however, was not statistically significant (P = .09). Figure 3 illustrates the 70% long-term remission duration for the 34 complete responders aged 20 to 49 who had low initial WBC counts. The remission duration was not found to be associated with FAB morphology, cell-surface markers, initial blast percentage, or patient sex.

Response data. One hundred fifteen (68%) of all eligible patients achieved complete remission (CR). Twenty-nine patients (17%) died early in the induction phase, before their remission status could be ascertained. Twenty-four patients (14%) failed to respond to therapy. CR rates were adversely influenced by advancing age. A 79% CR rate was achieved in patients under the age of 50 years, compared to a 35% CR rate in those 50 years of age or older. This difference is highly statistically significant (P < .0001). Compared with patients whose cells lacked expression of CD10, patients with common ALL had a higher CR rate, but this difference was not statistically significant. Patients with T-ALL had a CR rate of 90% (9/10), whereas patients with null-ALL had a CR of 45% (5/11). Owing to the small numbers in each group, these differences did not reach statistical significance. Sex, race, initial WBC count, initial blast percentage, and FAB morphology had no significant influence on CR rates in this study.

Remission duration. The overall remission duration estimates are depicted in Fig 1. The median duration of CR

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Bone marrow transplant patients were censored at the time of transplant.

Abbreviations: NR, median not reached; NE, not estimable because of small numbers of patients; NA, not applicable.

*P values from chi-square test for complete response rates.
†P values from log-rank test for survival, relapse-free survival and remission duration.
‡P values compare reviewed FAB L1, L2 only.
§P values compare common v other markers.
tial WBC counts of less than 15,000 had a median RFS of 24.0 months, compared with a median RFS of 12.1 months for patients with initial WBC counts of 15,000 or more. This difference was not statistically significant (P = .12). A Cox regression model was used to examine these factors simultaneously. Age was the only statistically significant factor identified (P = .01). Initial WBC count was not significant after adjusting for age (P = .11). However, as shown in Fig 4, a 58% long-term RFS is seen in the complete responders aged 20 to 49 with initial WBC counts of less than 15,000.

Cell-surface markers, initial blast percentage, the time from start of treatment to the time of complete remission, and patient sex did not show a statistically significant association with RFS. Fifty-seven patients with FAB L1 morphology had a median RFS of 21.8 months, and 38 patients with FAB L2 had a median RFS of 13.2 months. These differences, however, are not statistically significant (P = .27).

Overall survival. The median survival for all 168 eligible patients is 17.7 months (Fig 5). Patient age is significantly associated with survival (P < .001). The median survival for patients aged 15 to 19, 20 to 49, and 50 or older is 42.8, 21.0, and 1.1 months, respectively. A Cox regression analysis of survival showed age to be the only significant prognostic factor (P < .001). Adjusting for age, initial WBC count was not significant (P = .25).

Median survival time did not differ significantly between patients whose blasts expressed CD10 (20.1 months) and those who did not (12.7 months) (Table 2). Patients with T-ALL had a median survival of 37 months from the start of therapy, compared with 7.1 months for patients with null-ALL. Because of the small numbers in each group, these
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Patient's or physician's decision (five patients). Complications attributed to the reservoirs included grand mal seizures (three patients), hemiparesis (one patient), cranial nerve palsy (one patient), infection (one patient), and transient headache (two patients). One reservoir had to be replaced because of malfunction. One patient with an Ommaya reservoir suffered a fatal intracerebral hemorrhage, which was attributed to profound thrombocytopenia.

Relapses. Sixty-two of the 115 patients who achieved CR have relapsed. Eleven relapses occurred within 3 months of the date of CR, 10 from 3 to 6 months, 15 between 6 and 12 months, 17 in the second year, and nine after 2 years. The sites of relapse were bone marrow (46), CNS (8), combined marrow and CNS (5), and other (3: mediastinum [1], lymph nodes [1], and liver and adrenals [1]). There have been no documented testicular relapses among male patients.

DISCUSSION

The advent of intensive combination chemotherapy has improved the complete remission rate in adults with ALL under the age of 50, but the challenge remains to improve the long-term survival of patients with this disease. Hoelzer et al, using a more intensive regimen, have reported a CR rate of 77.8% in 162 adults with ALL, with a median remission duration of 20 months and a median survival of 26 months.

More recently, Gingrich et al, using a modification of the L-10M regimen of MSKCC reported a remission rate of 81% in 48 consecutive adults with ALL, with a median remission duration of 129 weeks and a projected median survival of at least 310 weeks. The most promising data, however, have been those of the L-10/L-10M protocols of MSKCC, with a remission duration of 51 months and a median survival of 53 months in 73 patients. We initiated our own trial to test the L-10M regimen in a multiinstitutional setting without excluding patients with respect to age or cytogenetic status.

In a previous pilot study by the SWOG, 25 adults with ALL were induced with vincristine, prednisone, and Adriamycin followed by maintenance therapy with 6-mercaptopurine and methotrexate with monthly reinforcements of vincristine and prednisone. Eighteen patients (72%) achieved complete remission. However, the median duration of remission was only 10.2 months. The results achieved in the current study represent an improvement in the treatment of adult ALL in the group, especially in patients under 50 years of age.

The overall CR rate of 68% in our study reflects the poor results in patients over 50 years of age (35% v 79% for patients under 50). The median durations of remissions and RFSs (22.9 and 20.9 months, respectively) compare quite favorably with the results obtained with other intensive treatment regimens. However, the superior results of the L-10M regimen reported from MSKCC were not duplicated. Two factors may have contributed to the discrepancy between our results and those from MSKCC. Forty patients (23.8%) in our study were over 50 years of age, as compared with 9.6% in the MSKCC study. A shorter survival in the L-17/17M protocol of 21 months was attributed mainly to a higher percentage of patients over the age of 50 (22%). Comparison of the two results is further complicated by the

differences did not have statistical significance. No differences in the survival distributions were seen according to initial blast percentage, patient sex, or initial WBC count.

Toxicity. The major toxicities encountered during the induction and consolidation phases of this study were leukopenia, thrombocytopenia, and infection. Twenty-nine patients died during the induction phase before their remission statuses could be ascertained. Only nine of these patients were under the age of 50. Twenty of 40 patients above the age of 50 died during induction. Fifteen patients died before they received any Adriamycin. The causes of death were infection (20 patients), hemorrhage (five patients), cardiac (two patients), and unknown (two patients).

Infection accounted for 15 of 20 early deaths in patients above 50 years of age. Seven deaths were due to gram-negative septicemia and six were due to pneumonia. The exact site of infection was not identified in two patients. Twelve of these patients were placed on broad-spectrum antibiotics, whereas three of them were initially treated with a single antibiotic. Antibiotic coverage was interrupted in three of the patients while they were still neutropenic. Masked infection, possibly due to steroids, may have delayed antibiotic therapy in two of the patients.

The first cycle of cytosine arabinoside and methotrexate during consolidation was followed by profound leukopenia and thrombocytopenia in the vast majority of patients, necessitating dosage reductions in the subsequent cycles. Five patients died during consolidation as a result of marrow toxicity (four of infection, one of hemorrhage). Two patients were removed from the study while in CR at the end of the induction phase; one developed disseminated candidiasis and the other developed obstructive jaundice due to a cholangiocarcinoma.

Forty-nine patients with a WBC count $\geq 20,000$ achieved complete remission. Ommaya reservoirs were implanted in 29. The other 20 patients did not have a reservoir for the following reasons: removal from study at the time of CR for bone marrow transplantation (five patients), early relapse (four patients), sepsis (three patients), small ventricles (two patients), intracranial hemorrhage (one patient), and

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fact that patients with Philadelphia chromosome–positive ALL were excluded from the MSKCC study, whereas patients were included in our study regardless of the cytogenetic status of their disease.

Morphologic evaluation performed thus far on 83% of the patients has revealed a predominance of L2 morphology, a finding similar to that of the MSKCC but unlike findings in other reports.14,16-18 In general, the distribution of immunologic subclasses in the 72 patients phenotyped is similar to distributions reported recently in other studies of adult ALL.19-28

Several prognostic factors have been reported in previous studies of ALL. These include age,14,17,18,22,27-30 sex,18,30 WBC count,4,6,14,16,18,27-30 percent of circulating blasts,6 degree of bone-marrow infiltration,29 hepatosplenomegaly,31 tumor presentation,16,18,29,31 FAB morphology,24,30,32-39 immunologic phenotype,4,17,23,30,33,34 CNS prophylaxis,17 chromosomal abnormalities,6,33-37 and time to complete remission.46

Age has generally been recognized as a major factor in determining the CR rate, with patients over the age of 50 having lower remission rates than younger patients, as was clearly the case in our study. With a few exceptions,16,17,27 longer remission durations and survivals have been reported in younger patients. A higher incidence of relapse, though not statistically significant, is apparent in patients between ages 15 and 19 compared with those between 20 and 49 years of age. This contrasts with the MSKCC experience and that of the German cooperative study group.6,46 This discrepancy cannot be explained on the basis of other prognostic factors. A similar trend seems to have been encountered by others. Thus, Gingrich et al and Omura et al reported a median remission duration of 14.7 months and 72 weeks for patients between 15 and 19 years of age, compared with 20.4 months and 129 weeks for patients over 20 years of age.14,17 It should be emphasized that none of these findings were of statistical significance. A thorough cytogenetic and phenotypic evaluation might have elucidated an exceptional high-risk category within this group of patients. On the other hand, a group of 34 responders between the ages of 20 and 49 who had low WBC counts emerges as having an exceptionally good prognosis. Seventy percent of these patients remain in continuous CR with a 58% RFS.

The preponderance of men in our study does not seem to have influenced the overall results, as there was no difference in CR rate or duration of survival between the two sexes. A higher CR rate and survival for women was reported by Baccarani et al18 but not by others.4,6,28,30

The WBC count did not influence the CR rate in our study and even though patients with WBC counts of more than 30,000/μL had a shorter CR duration, RFS, and overall survival than did patients with WBC counts of less than 30,000/μL, this difference is not statistically significant. A lack of prognostic value for WBC count was also reported by Omura et al17 and Leimert et al.30 In the series from MSKCC, WBC count did not influence CR rate but significantly influenced remission duration and survival.6 In addition, percentage of circulating blasts was a significant prognostic factor in the MSKCC series, a finding that could not be confirmed.

Patients with common ALL have previously been reported to have a better survival than those with null-, B-, and T-cell type ALL.4 Such an advantage could not be demonstrated in our study.

The incidence of chromosomal abnormalities could not be evaluated in our study, since chromosomal analysis was not routinely performed. However, no patient with a documented chromosomal abnormality was excluded. Since Philadelphia chromosome–positive ALL may account for up to 20% of all adult ALL,6,39 the inclusion of these patients may have adversely influenced the results in our study, in view of the poor prognosis for this group of patients.6,32,33,36

The patterns of relapse, similar to those found in other studies,6,33 with the prominence of early bone-marrow relapse, point to the need for alternative drug combinations during the early phases of therapy. This approach is being pursued in the current SWOG protocol, with a special emphasis on cytogenetic and immunologic studies of the disease.

REFERENCES
8. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Granlich HR, Sultan C, the French-American-British (FAB) Cooperative Group: The morphologic classification of acute lympho-
TREATMENT OF ADULT LYMPHOBLASTIC LEUKEMIA


35. Levin MD, Michael PM, Garson OM, Tillemann K, Firk FC: Clinicopathological characteristics of acute lymphoblastic leukemia with the 4;11 chromosome translocation. Pathology 16:63, 1984


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KK Hussein, S Dahlberg, D Head, CC Waddell, L Dabich, JK Weick, F Morrison, JH Saiki, E Metz and SE Rivkin