A Five-Drug Remission Induction Regimen With Intensive Consolidation for Adults With Acute Lymphoblastic Leukemia: Cancer and Leukemia Group B Study 8811


The goal of this phase II multicenter clinical trial was to evaluate a new intensive chemotherapy program for adults with untreated acute lymphoblastic leukemia (ALL) and to examine prospectively the impact of clinical and biologic characteristics on the outcome. One hundred ninety-seven eligible and evaluable patients (16 to 80 years of age; median, 32 years of age) received cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase; 167 patients (85%) achieved a complete remission (CR). CR was estimated to be about 50 months. Fifteen patients had refractory disease, and 17 (9%) died during induction. A higher CR rate was observed in younger patients (94% for those <30 years old, 85% for those 30 to 59 years old, and 39% for those ≥60 years old), and in those who had a mediastinal mass (100%) or blasts with a T-cell immunophenotype. Eighty percent of B-lineage and 97% of T-cell ALL patients achieved a CR (P < .001). The coexpression of myeloid antigens did not affect the response rate or duration. Seventy percent of those with cytogenetic or molecular evidence of the Philadelphia (Ph) chromosome and 84% of those without such evidence achieved a CR (P = .11). Patients in remission received multiagent consolidation treatment, central nervous system prophylaxis, late intensification, and maintenance chemotherapy for a total of 24 months. After a median follow-up time of 43 months, the median survival for all 197 patients is 36 months; the median remission duration for the 167 CR patients is 29 months. Favorable pretreatment characteristics relative to remission duration or survival are younger age, the presence of a mediastinal mass or lymphadenopathy, a white blood cell count (WBC) less than 30,000/µL, L1 morphology, T or TMy immunophenotype, and the absence of the Ph chromosome. The estimates of the proportion surviving at 3 years are 69% for patients less than 30 years old, 39% for those 30 to 59 years old, 89% for those who had a mediastinal mass, 59% with WBC less than 30,000/µL, 63% with L1 morphology, 69% for T or TMy antigen expression, and 62% for those who lack the Ph chromosome. Fifteen patients (8%) had no unfavorable prognostic factors and have an estimated probability of survival at 5 years of 100% (95% confidence interval, 77% to 100%). This intensive chemotherapy regimen produces a high remission rate and a high proportion of durable remissions in adults with ALL.

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ALTHOUGH RECENT clinical trials have shown that 65% to 85% of adults with acute lymphoblastic leukemia (ALL) may achieve a complete remission (CR), these remissions have been disappointingly short, especially for older adults.1,2 Recent treatment strategies have focused on increasingly intensive induction and postremission treatment with multiple chemotherapy regimens and also on multivariate analyses of prognostic factors to individualize therapy. Among the clinical and biologic characteristics that have been found to have prognostic importance for adults with ALL are age, initial white blood cell count (WBC), platelet count, serum lactate dehydrogenase and albumin levels, the presence of adenopathy or hepatosplenomegaly, performance status, immunophenotype, cytogenetics, and time to achieve CR.3,5

Investigators at single institutions have reported favorable results using intensive and prolonged remission consolidation programs. At the Memorial Sloan-Kettering Cancer Center, multiple courses of eight drugs were used in various combinations in the L-10 and L-10M protocols; a CR rate of 85% was reported among 72 patients.6,7 The median remission duration was 51 months, and disease-free survival at 5 years was estimated to be 45%. However, the median remission duration was 23 months. A similar program tested in 59 consecutive patients at the University of Iowa showed a CR rate of 75%; the median duration of remission was about 50 months.7 Fifteen patients (34%) remained in continuous remission longer than 5 years. These results and others have suggested that additional initial cytoreduction followed by multigagent intensification regimens extending over a number of months or years may offer the greatest likelihood for producing long-term disease-free survival for adults with ALL.10

The goal of this study was to evaluate a new intensive chemotherapy program for adults and to examine prospectively the impact of clinical and biologic characteristics on the outcome. This Cancer and Leukemia Group B (CALGB) study of adults with ALL tested the feasibility of the direct

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application of treatment programs that have proven to be very effective in high-risk childhood ALL. To achieve more rapid cyto reduction, our protocol used a five-drug induction regimen that was derived by adding a single dose of cyclophosphamide (1,200 mg/m²) to a slight modification of the four-drug regimen used in two previous CALGB studies (7612 and 8011). A similar five-drug induction program, when used in high-risk childhood ALL (Children’s Cancer Group study CCG-192P), yielded a CR rate of 96% with only 2% deaths during induction. We modified the standard consolidation program used in the German (Berlin-Frankfurt-Munster [BFM]) multistage trial for adults by increasing the dose of cyclophosphamide from 600 to 1,000 mg/m² and adding 2 weeks of vincristine and L-asparaginase treatment during the expected period of myelosuppression. To maintain maximum dose intensity, no dose reductions nor delays were permitted for myelosuppression in the absence of fever or infection. In addition, earlier and more extensive use of L-asparaginase was prescribed in this protocol than has commonly been used in adult ALL treatment programs (biweekly administration for 7 weeks during the first 12 weeks of therapy).

MATERIALS AND METHODS

Patients. Patients were eligible if they had untreated ALL of any of the three French-American-British (FAB) subtypes or acute undifferentiated leukemia. Patients were registered by telephone with the CALGB Statistical Office before treatment. The diagnosis of ALL was confirmed by central review of blood smears and bone marrow (BM) specimens for cytologic and cytochemical features according to the FAB criteria. Central immunophenotyping and pathology review were required. It was recommended that pretreatment blood and BM specimens be submitted for cytogenetic analysis, including central review of the karyotypes (CALGB study 8461), and for molecular analysis for the presence of the BCR gene (CALGB study 8762). Leukemia cells were analyzed in a central laboratory by Southern blot and pulsed-field gel electrophoresis for rearrangements within the BCR gene according to previously published methods, using conditions that will detect both the p190 and p210 subtypes. A lumbar puncture for spinal fluid examination was not recommended at diagnosis for asymptomatic patients. However, patients with symptomatic central nervous system (CNS) leukemia were not excluded but received additional CNS therapy. All patients were older than 15 years, had adequate renal and hepatic function (less than twofold elevated above the normal range unless felt to be caused by leukemia infiltration), and had provided informed consent.

Immunophenotyping (CALGB study 8364) was performed in two central CALGB laboratories. In 10 cases in which the pretreatment specimen was not evaluable in the central laboratory, immunophenotyping data from the local institutions were used after central review. Flow cytometric analysis and a panel of monoclonal antibodies were used for indirect immunofluorescence. The criterion for surface marker positivity was expression by at least 20% of the leukemia blast cell population. B-lineage antigen expression was defined as CD19 or CD20 positivity; T-lineage antigen expression as CD5 or CD2 reactivity; and myeloid antigen expression as CD13 or CD33 positivity. Expression of the common ALL antigen (CALLA) was assessed by CD10 reactivity. Cases expressing combinations of both B-lineage and T-lineage antigens were classified as BT, BTMy, or miscellaneous. Cases expressing surface membrane Ig (SmIg) were considered FAB-L3 (Burkitt-type ALL) and were not included among the other B-lineage cases in subsequent analyses. Patients with myeloperoxidase-negative blasts that expressed only myeloid antigens (and not B- or T-lymphoid antigens) were reclassified as acute myeloid leukemia (AML), subtype M0, and were deemed to be ineligible (4 patients).

Treatment protocol. The drugs and dosages used in the induction, consolidation, and maintenance phases of treatment are listed in Table 1. The induction course used a single dose of cyclophosphamide on day 1, 3 consecutive days of daunorubicin, weekly vincristine, biweekly L-asparaginase, and 3 weeks of prednisone. Before each L-asparaginase injection, the serum amylase activity was measured. In addition, it was recommended that fresh frozen plasma or cryoprecipitate be transfused to keep the fibrinogen level greater than 100 mg/dL. Initially, there were no dose reductions for older patients. After 1 year of accrual to the study (76 patients), one-third dose reductions were implemented for patients older than 60 years for the cyclophosphamide and daunorubicin and the prednisone therapy was shortened to 7 days, because of a high induction death rate caused by infection in this age group.

Early intensification (course II) included 2 months of treatment using cyclophosphamide, subcutaneous cytarabine, oral 6-mercapto purine (6-MP), vincristine, and more subcutaneous L-asparaginase. Two years after the study opened (156 patients), the protocol was amended so that CNS prophylaxis was initiated with the first two doses of intrathecal methotrexate during course II, rather than as previously performed in course III, to provide earlier CNS prophylaxis.

In course III, the CNS prophylaxis was completed with cranial irradiation (2,400 cGy) and 5 weekly doses of intrathecal methotrexate with daily 6-MP, followed by a brief maintenance period using daily oral 6-MP and weekly oral methotrexate. Course IV was a late intensification course lasting 8 weeks, followed by prolonged maintenance treatment with daily 6-MP and weekly methotrexate plus monthly pulses of vincristine and prednisone.

The total duration of treatment was 24 months. Testicular biopsies were not required at the end of therapy, and testicular irradiation was not administered prophylactically. Patients who had an isolated CNS relapse while continuing in a marrow remission were counted as failures; however, they continued to receive systemic chemotherapy on protocol after suppression of cerebrospinal fluid (CSF) lymphoblasts with additional intrathecal chemotherapy.

No hematopoietic growth factors were used. Cotrimoxazole or aerosolized pentamidine were recommended for Pneumocystis prophylaxis, starting in course III. The use of oral nonabsorbable antibiotics, the management of febrile episodes and transfusions, and the use of hospitalization were not prescribed by the protocol, but were rather left to institutional guidelines.

Data audit. CALGB central data management personnel were responsible for quality assurance for all clinical data submitted for this study. Eligibility criteria were verified for all patients and an evaluation of treatment, response, and toxicity was made by the study chair (R.A.L.). In addition, as part of the group data monitoring program, members of the CALGB Data Audit Committee made periodic site visits to all institutions to verify compliance with federal regulations and protocol requirements, including eligibility, treatment, response data, and follow-up. A random subset of 68 patients (32%) treated on this study had such an on-site review of their medical records. In addition, all radiotherapy portals and dosimetry records for the cranial irradiation were centrally reviewed for quality control by the Quality Assurance Review Center (Providence, RI).

Criteria for response. Patients were considered to be in CR when the neutrophil count was greater than 1,500/μL, the platelet count was greater than 100,000/μL, the results of BM examination were normal (including <5% blasts and >25% cellularity), and all extramedullary disease had resolved. Patients with greater than 25%...
INTENSIVE TREATMENT FOR ADULT ALL

Course cytogenetics, and molecular analysis were assessed with respect to INTENSIVE TREATMENT FOR ADULT ALL

omegaly, lymphadenopathy, FAB classification, immunophenotype,

cance of age, WBC count, platelet count, mediastinal mass, organ-

than the smallest possible time. Differences in survival or remission confidence intervals (CI) for these probabilities and the median statistic, adjusted for multiple comparisons where appropriate.

Median follow-up time was estimated by reversing the codes for the censoring indicator in a Kaplan-Meier analysis. In instances in which the median was not defined, the estimate was reported to be greater than the smallest possible time. Differences in survival or remission duration between patient subgroups were tested using the logrank statistic, adjusted for multiple comparisons where appropriate.

In accordance with the study objectives, the prognostic significance of age, WBC count, platelet count, mediastinal mass, organ-omegaly, lymphadenopathy, FAB classification, immunophenotype, cytogenetics, and molecular analysis were assessed with respect to CR rate and duration and survival. For the joint analysis of these variables, regression analyses were used. The analysis of CR rate was performed using the logistic regression model, whereas the analysis of CR duration and survival were performed using the Cox proportional hazards regression model. These were performed using the SAS procedures LOGISTIC and PHREG, respectively. For the regression analyses, all variables that attained a univariate P value of .20 or less were considered in the variable selection process. All reported P values are nominal two-sided values unless otherwise stated. The analysis was based on all data available as of August 4, 1994.

RESULTS

Patient accrual. Between September 1988 and June 1991, 214 patients were entered on CALGB study 8811 from 25 main member institutions and 41 of their affiliated hospitals. One patient withdrew before beginning treatment and 16 patients were judged ineligible after central review of all data (14 with AML and 2 with lymphocytic lymphoma). Thus, 197 patients were eligible and evaluable for this report.

Patient characteristics. The 197 eligible patients ranged in age from 16 to 80 years, with a median age of 32 years. Eighteen patients (9%) were 60 years or older. There were 124 men (63%) and 73 women. Eighteen patients were Afri-

### Table 1. Chemotherapy Regimen for ALL in Adults

<table>
<thead>
<tr>
<th>Course I: Induction (4 wk)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Cyclophosphamide*</td>
<td>IV</td>
<td>1,200 mg/m²</td>
<td>Day 1</td>
</tr>
<tr>
<td>Daunorubicin*</td>
<td>IV</td>
<td>45 mg/m²</td>
<td>Days 1, 2, 3</td>
</tr>
<tr>
<td>Vincristine</td>
<td>IV</td>
<td>2 mg</td>
<td>Days 1, 8, 15, 22</td>
</tr>
<tr>
<td>Prednisone*</td>
<td>PO/IV</td>
<td>60 mg/m²/d</td>
<td>Days 1-21</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>SC</td>
<td>6,000 IU/m²</td>
<td>Days 5, 8, 11, 15, 16, 22</td>
</tr>
</tbody>
</table>

*For patients ≥60 yr old:

Cyclophosphamide 800 mg/m² | Day 1 |
Daunorubicin 30 mg/m² | Days 1, 2, 3 |
Prednisone 60 mg/m²/d | Days 1-7 |

Course II: Early intensification (4 wk, repeat once)

| Intrathecal methotrexate | 15 mg | Day 1 |
| Cyclophosphamide | IV | 1,000 mg/m² | Day 1 |
| 6-Mercaptopurine | PO | 60 mg/m²/d | Days 1-14 |
| Cytarabine | SC | 75 mg/m²/d | Days 1-4, 8-11 |
| Vincristine | IV | 2 mg | Days 15, 22 |
| L-asparaginase | SC | 6,000 IU/m² | Days 15, 18, 22, 25 |

Course III: CNS prophylaxis and interim maintenance (12 wk)

| Cranial irradiation | 2,400 cGy | Days 1-12 |
| Intrathecal methotrexate | 15 mg | Days 1, 8, 15, 22, 29 |
| 6-Mercaptopurine | PO | 60 mg/m²/d | Days 1-70 |
| Methotrexate | PO | 20 mg/m² | Days 36, 43, 50, 57, 64 |

Course IV: Late intensification (8 wk)

| Doxorubicin | IV | 30 mg/m² | Days 1, 8, 15 |
| Vincristine | IV | 2 mg | Days 1, 8, 15 |
| Dexamethasone | PO | 10 mg/m²/d | Days 1-14 |
| Cyclophosphamide | IV | 1,000 mg/m² | Day 29 |
| 6-Thioguanine | PO | 60 mg/m²/d | Days 29-42 |
| Cytarabine | SC | 75 mg/m²/d | Days 29-32, 36-39 |

Course V: Prolonged maintenance (until 24 mo from diagnosis)

| Vincristine | IV | 2 mg | Day 1 of every 4 wk |
| Prednisone | PO | 60 mg/m²/d | Days 1-5 of every 4 wk |
| Methotrexate | PO | 20 mg/m² | Days 1, 8, 15, 22 |
| 6-Mercaptopurine | PO | 60 mg/m²/d | Days 1-28 |

lymphoblasts remaining in the BM after course I were removed from this protocol. All patients were required to have achieved a CR by half-way through course II to remain on the study.

Statistical methods. The proportion of patients achieving a CR to the induction regimen was the primary outcome measure on this study. The duration of CR and length of survival were additional outcome measures. Differences in proportions of CRs among patient subgroups were analyzed using Fisher’s exact test. The duration of CR was defined to be the time from achieving a CR to relapse (bone marrow, blood, CNS, or testicular), death, or date of last follow-up. Patients still at risk, lost to follow-up, or withdrawn for BM transplant (BMT) were censored for the analysis of remission duration. Survival was defined as the time from study entry to death or date of last follow-up. Probabilities of surviving and remaining in CR were estimated by the Kaplan-Meier method. Ninety-five percent confidence intervals (CI) for these probabilities and the median survival times were obtained using the method of Simon and Lee. Median follow-up time was estimated by reversing the codes for the censoring indicator in a Kaplan-Meier analysis. In instances in which the median was not defined, the estimate was reported to be greater than the smallest possible time. Differences in survival or remission duration between patient subgroups were tested using the logrank statistic, adjusted for multiple comparisons where appropriate.

In accordance with the study objectives, the prognostic significance of age, WBC count, platelet count, mediastinal mass, organ-omegaly, lymphadenopathy, FAB classification, immunophenotype, cytogenetics, and molecular analysis were assessed with respect to CR rate and duration and survival. For the joint analysis of these variables, regression analyses were used. The analysis of CR rate was performed using the logistic regression model, whereas the analysis of CR duration and survival were performed using the Cox proportional hazards regression model. These were performed using the SAS procedures LOGISTIC and PHREG, respectively. For the regression analyses, all variables that attained a univariate P value of .20 or less were considered in the variable selection process. All reported P values are nominal two-sided values unless otherwise stated. The analysis was based on all data available as of August 4, 1994.
can-American, 4 were Hispanic, and 1 was Asian. Initial WBC counts ranged from 500 to 475,000/µL (median, 17,000/µL), platelet counts ranged from 8,000 to 557,000/µL (median, 55,500/µL), and hemoglobin levels ranged from 4.0 to 16.6 g/dL.

Thirty-four percent of patients had WBC counts ≥30,000/µL, 13% had WBC counts greater than 100,000/µL, and 6% had more extreme hyperleukocytosis with WBC counts in excess of 200,000/µL. Fifty-six percent of patients had a fever or infection before chemotherapy. Only 1 patient had symptomatic CNS disease at diagnosis. Thirty patients (15%) had a mediastinal mass, 60 (31%) had palpable splenomegaly, and 47 (24%) had hepatomegaly. Palpable lymphadenopathy was present in 78 patients (40%).

One hundred sixty-six patients (84%) could be classified by the pathology review committee using the FAB criteria; 71 cases (43%) were L1, 87 (52%) were L2, and 8 (5%) were L3. Morphologic subtyping could not be accomplished in 24 cases, usually because of inadequate marrow aspirate samples, and these were considered unclassifiable acute leukemia. Seven cases were not evaluable for central review.

Central immunophenotyping was successfully performed in 130 cases. Where these determinants were missing, local institutional immunophenotyping data were used in 10 cases to assess the lymphocyte surface marker profile. Excluding the 8 patients with L3 ALL, there was surface expression of at least one B-lineage antigen in 86 cases (61%). Thirty-nine cases (28%) expressed at least one T-lineage antigen and 27 cases (19%) expressed at least one myeloid (My) antigen. Five subsets were defined: pure B lineage, 67 cases (48%); BMy, 19 cases (14%); pure T lineage, 31 cases (22%); TMy, 8 cases (6%); and a miscellaneous group with other marker profiles (SmIg positive, BT, BTMy, and unclassified), 15 cases (11%). The miscellaneous group was not included in further analyses by immunophenotype. Sixty-five percent of the T or TMy patients had a mediastinal mass, compared with only 4% of the non-T-lineage patients. Eighty-three percent of patients with a mediastinal mass had a T or TMy immunophenotype.

Eighty-five (73%) of the 116 cases submitted for cytogenetics were evaluable after central review of the karyotypes. The Philadelphia (Ph) chromosome was identified in 25 patients (29%). Molecular analyses for a BCR gene rearrangement from pretreatment blood and/or marrow specimens were performed in 77 cases; 20 (26%) were positive. Table 2 shows the results from these two analytic techniques. When the results of both cytogenetic and molecular tests were combined, 30 patients were positive for either the Ph chromosome or BCR-ABL rearrangement (Ph-positive ALL). Forty-nine patients were analyzed by both methods: 15 were positive and 29 were negative by both tests (90% concordance). Eighty-three patients were negative by at least one test (and not positive by the other). Thus, approximately 27% of the 113 patients studied had Ph-positive ALL. Forty percent of patients with B-lineage ALL were Ph-positive, compared with 5% of those with T-lineage ALL.

Remission induction. One hundred sixty-seven (85%) of 197 eligible patients achieved a CR (Table 3). One hundred twenty-three (74%) of the responders were in CR within 30 days from the first treatment; 44 (26%) required more than 30 days, either because of slow recovery of marrow cellularity and blood counts in 29 patients or because additional chemotherapy (ie, course II) was required in 15 patients. Eighty-eight percent of remissions were achieved within 42 days. Eight patients (4%) had no response to induction chemotherapy (ie, >25% lymphoblasts persisting in the marrow) and were taken off study after 4 weeks. Five patients (3%) had at best only a partial response and were taken off study after 8 weeks. Of these 13 patients with refractory disease, 5 are known to have had a Ph chromosome or BCR rearrangement, 1 had a t(4;11), and 1 had Burkitt-type (L3) ALL. Despite additional treatment, all but 1 (who received an allogeneic marrow transplant) have died.

Seventeen patients (9%) died before hematopoietic recovery from the induction chemotherapy: 1 of these was less than 30 years old (1% of the age cohort), 7 were 30 to 59 years old (8%), and 9 were ≥60 years old (50%). The predominant cause for induction mortality was infection with either enteric gram-negative bacteria, Streptococcus pneumoniae or Candida species, occurring during week 2 or 3 of treatment. There were two episodes of clinically severe tumor lysis syndrome, and 1 of these patients died.

Treatment response was a function of age (Table 4). Eighty-two of the 87 patients (94%) less than 30 years old achieved a CR, compared with 78 of 92 (85%) between 30 and 59 years of age and only 7 of 18 (39%) of those 60 years and older (P < .001). Four percent to 10% of patients within each age group had either a partial remission or no response to induction chemotherapy. After the protocol was amended to institute a one-third reduction of the chemotherapy doses for patients ≥60 years old (see Materials and Methods and Table 1), the CR rate for this older group

| Table 2. Results of Cytogenetics and Molecular Assays for Ph Positivity in Adult ALL |
|---------------------------------|-----------|-----------|-----------|-----------|-----------|
|                  | BCR Rearrangement (n) |-----------|-----------|-----------|-----------|
| Ph Chromosome     | Positive | Negative | Unknown   | Total (n) |
| Positive          | 15       | 2         | 8         | 25        |
| Negative          | 3        | 29        | 28        | 60        |
| Unknown           | 2        | 26        | 84        | 112*      |
| Total             | 20       | 57        | 120†      | 197       |

* Includes not done (n = 81) and not evaluable (n = 31).
† Includes not done (n = 114) and not evaluable (n = 6).

| Table 3. Results of Therapy |
|-----------------------------|-----------|-----------|
| Patients entered           | 214       |
| Patients eligible          | 197       |
| Induction deaths           | 17 (9%)   |
| Refractory disease         | 13 (7%)   |
| CR                          | 167 (85%) |
| Died in remission          | 10 (6%)   |
| Censored for BMT in first CR| 5 (3%)    |
| Relapsed                    | 77 (46%)  |
| CCR                         | 75 (45%)  |
changed from 3 of 10 to 4 of 8 because of fewer induction deaths (6 [60%] vs 3 [38%], respectively).

Subset analyses. The remission induction rate did not vary significantly by gender, performance status (0-1 vs 2-4), or the presence or absence of fever or infection, splenomegaly, or hepatomegaly (Table 4). The presence of a mediastinal mass or lymphadenopathy were favorable features associated with CR rates of 100% and 91%, respectively. The
patients overall (88% for 8 TMy patients and 74% for 19 in the marrow. The CR rate was 90% for patients with FAB treatment marrow cellularity or the fraction of lymphoblasts teen patients were studied by at least one genetic method. The CR rate was 70% for the 30 patients identified by one or both tests as having Ph-positive ALL and 84% for those who were negative by at least one genetic test and 65% for the 20 patients in whom a BCR-ABL rearrangement was detected. One hundred thirteen patients who achieved a CR within 30 days were estimated to remain in CR after 3 years, compared with 33% of those who needed longer than 30 days to enter remission, but this difference was not statistically significant (P = .24). Similarly, those 20 patients who required more than 42 days to achieve CR have not had significantly shorter remission durations (median, 26 months v 29 months for rapid responders, P = .62).

After adjusting for age in a logistic regression model, the WBC count retained statistical significance with respect to CR duration (P = .006). After controlling for these two factors, mediastinal mass was the most significant variable with respect to remission duration (P < .001). After adjusting for all three factors, FAB subtype (L1 vs L2) attained prognostic significance for CR duration (P = .005), as did immunophenotype (T or TMy vs others; P = .04), whereas adverse cytogenetics [the detection of Ph, or the BCR/ABL gene, or a t(4;11)] retained significance (P = .04). Among T or TMy patients, the WBC count did not have prognostic significance for CR duration, but a mediastinal mass was significantly associated with longer remission duration (P = .04).

Overall survival. The estimated median survival for all 197 treated patients is 36 months after a median follow-up time of 43 months (range, 24 to 64 months; Fig 2). The median survival for the 167 patients who achieved a CR has not been reached but is longer than 45 months. The survival on this study is significantly better than that observed on any of the three previous CALGB studies (P < .001 for all 3 comparisons); CALGB 8513 had a median survival of 19 months, and CALGB studies 7612 and 8011 had medians of 16 months (Fig 3).11,12,28

Patient age is significantly associated with survival (P <
.001). The probability of survival at 3 years is estimated to be 69% for those less than 30 years old, 39% for those 30 to 59 years old, and 17% for those ≥60 years old (Fig 4). Survival is significantly longer for patients presenting with a WBC less than 30,000/µL ($P = .001$). Among patients with high WBC counts, the median survivals are 24 months for those with 30,000 to 59,000/µL, 14 months with 60,000 to 99,000/µL, and 11 months with greater than 100,000/µL, but these are not significantly different. Despite a high CR rate, of the 25 patients with an initial WBC count greater than 100,000/µL, only 7 (27%) remain alive at last contact. Patients who achieved a remission within 30 days are no more likely to be alive at 3 years than those who required more than 30 days to achieve a CR (59% vs 56%).

Survival is associated with morphology and immunophenotype. The probability of survival at 3 years is estimated to be 63% for L1 and 45% for L2 ($P = .03$). The patients with L1 morphology had a median WBC count of 19,200/µL (range, 800 to 401,000/µL); 39% had T or TMy immunophenotypes and 20% were Ph positive. The L2 patients had a median WBC count of 17,200/µL (range, 700 to 328,500/µL); 21% had T or TMy immunophenotypes and 44% were Ph positive. The 8 patients with L3 morphology were considered as a separate FAB group but were not compared with the L1 or L2 patients because of the small sample size. Their median WBC was 9,100/µL (range, 1,600 to 31,300/µL) and none had a T or TMy immunophenotype or the Ph chromosome. These patients have had a short median survival (6 months). Although 3 patients survived longer than 2 years, 2 have relapsed and 1 of these subsequently received a BMT.

Survival is also influenced by immunophenotype: 38% at 3 years for those with the expression of B-lineage antigens compared with 69% for those with T-lineage antigen expression ($P = .001$; Fig 5). The myeloid antigen-positive cases have had an intermediate survival (55% at 3 years) but not statistically different from that of patients without myeloid antigen expression within the same lymphoid lineage.

Similar to its impact on remission duration, the detection of the t(9;22) has a statistically significant adverse effect on survival. Only 16% (95% CI, 7% to 32%) of those with either a Ph chromosome or a BCR-ABL rearrangement are estimated to survive for 3 years, compared with 62% of those who were negative by both genetic tests ($P < .001$).

In the multivariate analysis, after adjusting for age, WBC count retained statistical significance with respect to survival ($P < .001$). Among T or TMy patients, the WBC count did not have prognostic significance for survival, but a mediasti-
nal mass was significantly associated with longer survival ($P = .01$). After controlling for age, WBC count, and mediastinal mass, FAB subtype retained prognostic significance with respect to survival ($P = .001$). If cytogenetic abnormalities are accounted for first, then age, WBC count, and mediastinal mass continue to be significant.

**Toxicity.** The major toxicities encountered during the induction and consolidation phases of this study were myelosuppression and infection (Table 5). Seventeen patients (9%) died during the induction course, and most of these deaths were from infection with gram-negative bacteria or fungi. Nine of these patients were older than 60 years. There was 1 death from renal failure after tumor lysis syndrome during the induction phase.

Eleven patients (3 older than 60 years) died later, while in remission and receiving consolidation or maintenance chemotherapy. Six deaths were caused by infection, and 1 patient died after a colon perforation. Eleven patients were diagnosed to have *Pneumocystis carinii* pneumonia at some point during the 2 years of treatment; 1 of these patients died 3 weeks after the completion of all chemotherapy. There were 3 deaths from bleeding among patients in remission who were receiving additional chemotherapy: 2 hemorrhagic strokes and 1 gastrointestinal hemorrhage.

The L-asparaginase treatment was generally well tolerated. Several patients had local cutaneous reactions that did not recur when Erwinia L-asparaginase was substituted for the initial *Escherichia coli*-derived drug. Treating physicians were required to evaluate the patient’s serum amylase level before each L-asparaginase injection. Eight episodes of clinically significant pancreatitis were reported during courses I and II during the 7 weeks of L-asparaginase therapy. One patient had inferior vena cava thrombosis and another had a pulmonary embolism. Fatigue and malaise were common during L-asparaginase therapy; mental confusion was rare.

All patients were hospitalized during course I and many patients required hospitalization during courses II and IV for the treatment of fever while granulocytopenic. Otherwise, hospitalization was seldom necessary. Increases in the levels of hepatic transaminases were common and often required dose adjustments of maintenance chemotherapy. The treatment program was rigorous; 19 patients withdrew from the prescribed therapy because of severe but less-than-life-threatening toxicity. These patients continued to be observed until relapse and death. Three patients underwent allogeneic BMT in first remission; 2 of these have died. Two of the transplant patients had Ph-positive ALL; 1 relapsed after BMT and has died and the other is alive and free of disease more than 3 years after diagnosis. One patient underwent an autologous BMT in first remission, relapsed 6 months later, and died. A second patient, an 18-year-old man with Ph-positive ALL, underwent an autologous BMT in first remission followed by interferon therapy and was alive at last contact 14 months later. Two second cancers have been discovered, 1 renal and 1 breast carcinoma.

**Patterns of failure.** As described above, 28 patients (14%) died while undergoing treatment on this study. Treatment-related mortality was strongly related to increasing age and was most often the result of infection.

Twelve of the 13 patients who survived the induction chemotherapy but failed to achieve a CR have died despite additional therapy. One 19-year-old man had Ph-positive ALL that was refractory to this protocol therapy but has remained free of disease for longer than 1 year after an allogeneic BMT.

Of 19 patients in remission who withdrew voluntarily or on their physician’s advice because of toxicity before completing 2 years of the protocol therapy, 10 have experienced a relapse of ALL and 8 of these have died. However, 7 patients who did not complete the prescribed therapy remain alive with no evidence of disease. All 7 have now been in CCR longer than 3 years.

To date, 77 of the 167 patients (46%) who achieved a CR have experienced a marrow and/or CNS relapse of ALL. The minimum estimate of CNS relapse is 15% (25 patients). Follow-up CSF examinations were not always reported, but at least 7 patients have had concurrent relapses in the marrow and the CNS. Only one patient, a 53-year-old man with Ph-positive ALL, had neurologic symptoms and CSF lymphoblasts at diagnosis. Despite achieving a CR with induction chemotherapy, intrathecal methotrexate, and cranial irradiation, he suffered a BM and CNS relapse 4 months after diagnosis and died 3 months later.

For 18 patients, CNS relapse preceded evidence of BM relapse by more than 1 month (range, 1 to 19 months). These latter patients had various features previously associated with an increased risk of CNS leukemia: 5 had L3 morphology, 5 had Ph-positive ALL, 3 had T-cell ALL, and 8 (including 2 Ph-positive and 2 T-ALL cases) had greater than 30,000 WBC/µL at diagnosis. Initially on this study, asymptomatic patients underwent their first lumbar puncture for spinal fluid examination and intrathecal methotrexate at the beginning

| Table 5. Severe or Life-Threatening Toxicity During Treatment for ALL |
|---------------------------------|----------------|----------------|----------------|
|                                 | Induction | Intensification | Maintenance |
| Leukopenia (<2,000 µL)          | 99%       | 97%            | 75%         |
| Thrombocytopenia (<50,000/µL)   | 94        | 84             | 32          |
| Anemia (Hgb <8 g/dL)            | 65        | 84             | 26          |
| Hemorrhage                      | 5 (1)     | 4 (2)          | 0           |
| Infection                       | 54 (7)    | 49 (4)         | 25          |
| Fever without infection         | 4         | 8              | 2           |
| Nausea/vomiting                 | 8         | 17             | 8           |
| Stomatitis                      | 7         | 9              | 7           |
| Diarrhea                        | 4         | 3              | 1           |
| Hepatic                         | 25        | 28             | 30          |
| Pulmonary                       | 8         | 5 (1)          | 4           |
| Cardiac                         | 5 (1)     | 1              | 6           |
| Genitourinary                   | 8 (1)     | 2              | 1           |
| CNS                             | 6         | 13             | 6           |
| Peripheral nervous system       | 7         | 12             | 7           |
| Skin                            | 4         | 1              | 2           |
| Allergy                         | 0         | 1              | 1           |

The table lists the frequencies (%) of grade 3 and 4 toxicities during each phase of treatment using the CALGB Expanded Common Toxicity Criteria. The percentage of patients with lethal toxicity is shown in parentheses.
of course III, 3 months after diagnosis, when the BM was already in remission. Seven asymptomatic patients were discovered to have CSF lymphoblasts at that time. Isolated CSF disease was also discovered in three patients who developed neurologic symptoms while receiving consolidation chemotherapy in course II. Although most responded to intrathecal chemotherapy and cranial irradiation and several maintained a subsequent CR for longer than 1 year, all eventually suffered a BM relapse or died from recurrent CNS leukemia. After the protocol was amended so that intrathecal methotrexate was administered starting at the beginning of course II (see Table 1), there were fewer cases of early CNS leukemia observed (2 patients).

Six patients have had late isolated CNS relapses (without simultaneous BM relapse), occurring after more than 1 year in CR. Four relapses occurred while receiving maintenance chemotherapy and 2 occurred 2 and 4 months after completion of 2 years of therapy. All 6 have died, 3 after subsequent BM relapses. One 34-year-old man with T-cell ALL had an isolated testicular relapse 5 months after completing 2 years of therapy. He achieved a second CR after local irradiation and received additional systemic chemotherapy; he suffered a BM relapse 11 months later and died.

During the 24 months of treatment, 68 patients relapsed or died in remission. The risk of failure was greater for patients with Ph-positive or L3 ALL than for those with T-lineage or B-lineage ALL but lacking the Ph or L3 characteristics. When considering only B-lineage (not including Ph-positive or L3) versus T-lineage ALL cases, the risk of relapse was comparable throughout the 2 years of therapy. As yet, only 3 relapses have been observed among 50 patients in CR for longer than 3 years.

Of 30 patients identified to have the Ph chromosome or BCR-ABL rearrangement, 21 (70%) achieved a CR, but 16 of these have relapsed and died. Three others (39, 74, and 80 years old) have died in remission, and 1 is alive with no evidence of disease after a BMT. Only 1 patient (46 years old) has remained on study and continues in first remission for longer than 4 years.

Patients with a t(4;11) have been identified as a second cytogenetic group with a poor outcome. Two such patients were known to be enrolled on this study. One woman (64 years old; WBC 392,200/μL) died during induction and 1 man (61 years old; WBC 209,800/μL) had refractory disease and died 2 months after diagnosis.

**High-risk patients.** Groups of high-risk patients were identified by the presence of one or more of the following unfavorable characteristics: age ≥60 years, WBC count ≥30,000/μL, FAB L3 morphology, absence of a mediastinal mass, and the presence of Ph or t(4;11). Table 6 lists the numbers of patients with each of these features and their survival estimates. Fifteen patients (8%) had no unfavorable features; 100% of these patients are estimated to be alive at 5 years (95% CI, 77% to 100%). Eight male and 7 female patients comprised this favorable group. Their median age was 30 years (range, 16 to 39 years) and the median WBC count was 10,700/μL (range, 1,400 to 24,900/μL). Five had L1 morphology and 10 had L2. Eighty-three percent had a T or TMy phenotype. All had a mediastinal mass (by definition), 5 had splenomegaly, and 3 had hepatomegaly.

One hundred three patients (52%) had only a single known adverse feature; in 87, this was the absence of a mediastinal mass. Fifty-nine percent of these patients were alive at last follow-up. For this analysis, missing values were imputed as "no adverse feature," which has undoubtedly caused some underreporting of multiple adverse features, especially with respect to cytogenetics. For example, only 49% of the patients listed with one unfavorable feature had cytogenetic data available. Hence, we separated those patients with complete information ("exactly one adverse feature") from those with missing data and labeled the latter group as "one known adverse feature." No patient is considered to be high risk based solely on age. Patients known to have L3 morphology or unfavorable cytogenetics appear to have multiple other adverse features. There are no survivors among the 5 patients known to have four adverse features.

**DISCUSSION**

One major goal of this study was to achieve initial cytocr-duction as rapidly as possible, using five lymphocytotoxic drugs during the induction course. The fraction of patients who subsequently achieved a CR (85%) was the highest yet observed in a CALGB trial and compares favorably with the outcomes reported from the best, large, single-institution trials. The two preceding CALGB trials (8011 and 8513), enrolling unselected patients at the same centers with
an equivalent age distribution, had shown CR rates of 64% and 71%, respectively. Other recent multicenter trials have also reported lower CR rates: 74% for the German ALL trial (GMALL-01), 75% for GMALL-02, 68% for the SWOG trial, and 64% for the ECOG trial, despite median ages for the patients in each of these trials approximately 5 years younger than in the three CALGB trials. A recent Medical Research Council trial reported an 87% CR rate for patients with ALL, but that study included patients as young as 14 years old and 40% of the patients were less than 20 years old.

Among patients less than 30 years old, the CR rate of 94% in our study also exceeds the remission rates of 75% to 87% observed in other multicenter adult trials and approaches the 96% CR rate observed by the Children's Cancer Group using the same induction schedule for high-risk childhood ALL. Unfortunately, the response rate for patients more than 60 years old in our study was markedly affected by the high early death rate. Thus, the question of whether the poor overall outcome of older adults with ALL is caused by inability to withstand treatment or to chemotherapy resistance remains to be answered. However, once remission was achieved, the probability of continuing in CR at 3 years was not different between patients 30 to 59 years old and those older than 60 years, although the number of older patients was small.

Another objective of our trial was to provide the highest possible dose intensity of treatment during courses I and II after initial rapid cytodestruction. For that reason, no delays in treatment or dose reductions were permitted because of pancytopenia in the absence of fever or obvious infection. Nevertheless, on average, patients required 4 months to complete the first 3 months of scheduled therapy. We cannot determine whether the apparent success of this treatment program is the result of the initial rapid cytodestruction or the dose intensity of the later therapy.

Preliminary data from three randomized clinical trials suggest that the concurrent use of filgrastim (granulocyte colony-stimulating factor [G-CSF]) may improve the ability to deliver intensive chemotherapy more safely. The follow-up periods for these trials are still short, and the full impact of the use of G-CSF during the treatment of adults with ALL remains to be determined.

Modern chemotherapy regimens for ALL have evolved empirically in such a fashion as to make it difficult to conclude which part of the total therapy is most effective or, alternatively, even deleterious. Few randomized clinical trials have been performed. In this regard, it is important to note the results of the recent GIMEMA ALL-0288 trial, as yet published only in abstract form. Here, 541 patients between 12 and 65 years of age were randomly assigned to remission induction treatment with daunorubicin, vincristine, prednisone, and L-asparaginase with or without cyclophosphamide. Thus, one arm received the same five agents that we used in CALGB 8811. However, those investigators found no difference in the CR rates (80%) on each arm, calling into question the added benefit of the cyclophosphamide.

Patients with large-cell lymphoma whose disease responds more rapidly to chemotherapy have more durable remissions. Likewise, some studies of both childhood and adult ALL have shown that patients obtaining a more rapid response of their leukemia to induction therapy have a higher CR rate and longer disease-free survival. However, others have found that time to achieve remission was not predictive of prognosis. In our study, we did not observe a statistically significant difference in long-term outcome for the 27% of CR patients who required more than 30 days to enter remission. This finding might be explained by the fact that delay in achieving CR is a function both of drug resistance of the disease as well as myelotoxicity from the treatment.

It would appear that the use of a more intensive remission induction program has overcome the negative prognostic importance previously associated with the expression of myeloid surface antigens or with any delay in achieving CR for longer than 30 days. When we carefully excluded patients with minimally differentiated AML (FAB type M0), we found no significant differences in the response rates, remission duration, or survival of ALL patients who had coexpression of CD13 or CD33. In general, the course of these patients appeared to be determined by their lymphoid lineage, ie, B or T cell.

The TMy immunophenotype may identify a distinct subset with a favorable prognosis. We treated 8 such patients, all of whom were men. Their ages ranged from 17 to 46 years (median, 32 years). The median WBC count was 14,900/μL (range, 1,000 to 132,800/μL). Three had splenomegaly, but only 1 had a mediastinal mass. Three had L1 morphology, 3 had L2 morphology, and 2 were unclassified. None of the 7 studied had the t(9;22) by cytogenetics or by molecular assays. Seven (88%) achieved a CR; as yet, only 1 of these has relapsed and died. After 3 years, 86% remain in continuous CR and 75% of the overall group remain alive.

Fifteen percent of our patients had an enlarged mediastinum. Surprisingly, we found that this was predictive of a favorable outcome, with an influence on remission rate, duration of remission, and survival in multivariate analyses. Most previous studies of adult ALL have failed to identify mediastinal enlargement as an important factor. A trend similar to ours seemed apparent in an older German study, but it did not reach statistical significance. Furthermore, in our study, lymphadenopathy, another manifestation of leukemia mass, had a favorable effect on remission rate and survival in a univariate but not multivariate analysis. This favorable effect of mediastinal node enlargement may be caused in part by the favorable effect of the T-lineage immunophenotype, because 83% of the patients with an enlarged mediastinum had T or TMy disease, or of L1 morphology (41% of these patients). The median age of the patients with a mediastinal mass was 32 years (range, 16 to 54 years) and the median WBC count was 24,100/μL (range, 1,400 to 475,000/μL). None had the Ph chromosome.

Biologic characteristics of the disease continue to be powerful determinants of response. The use of molecular methods to detect the BCR-ABL rearrangement will reliably detect the approximately 30% of adults with ALL with a t(9;22). Despite a nearly equivalent CR rate, the disease-free survival of these patients is clearly inferior to those
without this genetic mutation. Indeed, once this subgroup was reliably identified and considered separately, the estimated 3-year survival of the remaining 31 B-lineage patients improved to 48% (95% CI, 32% to 65%). This was not significantly different (P = .13) from the survival of the 27 similarly evaluated patients with T-lineage disease (62%; 95% CI, 42% to 79%). As yet, no chemotherapy regimen has effectively cured patients with the Ph chromosome. In our study, only 16% (95% CI, 7% to 32%) are estimated to survive at 3 years. The proportion of patients with the Ph chromosome increases with age. Thus, this abnormality may be in part responsible for the poor prognosis of older adults with ALL. Recent data suggest that approximately one third of Ph-positive patients can be cured using allogeneic BMT. At this time, allogeneic transplantation early in first CR should be considered the treatment of choice for Ph-positive patients of suitable age.

Burkitt-type (L3) B-ALL also had a poor outcome using this treatment program. Approximately 5% of adults with ALL have this subtype, which is characterized by the t(8;14) or one of its variants, t(2;8) or t(8;22). Although 75% of our L3 patients achieved a CR, remissions were very short (median, 3 months) and 5 of the 6 patients have relapsed. Recent trials using short intensive chemotherapy programs with high doses of cyclophosphamide or ifosfamide and high-dose methotrexate and cytarabine have produced disease-free survival rates of 57% to 76% in children and adults with L3 ALL or Burkitt’s lymphoma.

Patients with FAB L2 morphology appear to do worse than those with L1, but it is not clear that L2 by itself can be considered a poor-risk group. Indeed, in our multivariate analyses, of 10 patients whose only adverse feature would have been L2 morphology, all are alive at the most recent follow-up. Patients with L3 morphology or adverse cytogenetics [Ph or t(4;11)] appear to have other adverse features and should be considered at high risk for treatment failure regardless of the known number of other adverse features. Complete data should be obtained at diagnosis to identify the risk profile of individual patients with ALL to assist in treatment planning.

In 23% of our patients who have relapsed, lymphoblasts were observed in the spinal fluid 1 to 19 months before a BM relapse and another 9% had simultaneous CNS and BM relapses. Despite further treatment, all but 3 of these patients have died. In our amended protocol, the first specific CNS treatment begins in course II, after achieving a BM response. It is likely that systemic cyclophosphamide, prednisone, and L-asparaginase provide some transarachnoid benefit during the induction course. However, the CSF appears to remain an important sanctuary site for ALL. Many of the CNS recurrences occurred in patients with previously described high-risk features for CNS involvement: Ph chromosome, L3 morphology, T-cell phenotype, or high initial WBC count. More intensive systemic chemotherapy, such as high-dose methotrexate or high-dose cytarabine, or higher radiation doses, such as 3,000 cGy to the cranium and perhaps to the entire spinal axis, might be appropriate for these poor-prognosis patients.

In summary, we report the results of a multi-institutional study supporting the usefulness of a dose-intense multicourse 2-year therapy program for adults with ALL. The CR rate is high, and for the younger than 30-year-old adult patients approaches that achieved in high-risk childhood ALL. The median survival has not been reached for younger patients; it is greater than 2 years even for those in the 30- to 59-year-old age group. Two subgroups have had particularly favorable outcomes: those with a mediastinal mass and those with a TMy immunophenotype. We have identified five patient characteristics that are related to adverse prognosis and found that patients with multiple adverse features appear to have an increased risk. This observation requires validation using other data sets. Future efforts should be directed toward designing innovative approaches to those patients with the identified adverse prognostic factors, especially older age and adverse cytogenetic/molecular biologic features.

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