Modified \( \text{LSA}_2\text{-L}_2 \) Treatment in 53 Children With E-Rosette-Positive T-Cell Leukemia: Results and Prognostic Factors (A Pediatric Oncology Group Study)

By D. Jeanette Pullen, Margaret P. Sullivan, John M. Falletta, James M. Boyett, G. Bennett Humphrey, Kenneth A. Starling, Vita J. Land, Paul G. Dyment, Tribhawan Vats, and Marilyn H. Duncan

In an attempt to improve the poor outlook for children with T-cell leukemia (T-ALL), the Southwest Oncology Group, Pediatric Division, used a modified \( \text{LSA}_2\text{-L}_2 \) multidrug regimen to treat 53 patients with E-rosette-positive T-ALL. This regimen was chosen because of its demonstrated efficacy in T-cell (mediastinal) non-Hodgkin's lymphoma. Complete remission (CR) rate was 88%. Range of follow-up for those patients remaining in CR is 24–49 mo (median 39 mo). Life table analysis estimates that 40% (SE 8.3%) of all patients who started induction therapy will remain failure-free at 3 yr. For patients achieving CR, 46% (SE 9%) are projected to remain in both marrow and extramedullary CR at 3 yr. Median failure-free duration was 13 mo, but only 1 patient has relapsed beyond 16 mo. Twenty-nine percent of initial relapses were isolated CNS relapses. The following presenting factors did not relate significantly to outcome: hemoglobin, platelet count, uric acid, race, and mediastinal mass. Age >10 yr was a poor prognosis indicator only in the <50,000/µl WBC group. Sex was not a significant factor after adjusting for WBC. WBC was the most important prognostic factor: 19% (SE 8%) of patients with WBC >50,000/µl are projected to remain failure-free at 3 yr as compared to 67% (SE 11%) of patients with WBC <50,000/µl. Although the overall results are better than those previously reported for pediatric patients with T-ALL, the long-term failure-free rate remains low for patients presenting with >50,000/µl WBC.

Children with T-cell acute lymphocytic leukemia (T-ALL) have a poorer prognosis than children with non-T, non-B acute lymphocytic leukemia (ALL). Treatment programs, which have proven highly effective for the majority of children with ALL, have produced significantly shorter durations of remission for pediatric patients with T-ALL.\(^1\)\(^-\)\(^11\)

The prognostic importance of T-cell leukemia identification became apparent in the mid 1970s. In 1976, the investigators of the Southwest Oncology Group (SWOG) Pediatric Division, now the Pediatric Oncology Group (POG), began to perform E-rosette testing on bone marrow cells from all pediatric patients with newly diagnosed ALL.\(^12\) This practice permitted early identification of patients with T-ALL so that detailed study of this small subgroup could be accomplished in a prospective manner.

Since all information then available suggested an extremely poor outlook for patients with T-ALL,\(^1\)\(^2\)\(^3\)\(^13\)\(^14\) the members of the SWOG, Pediatric Division in 1976 decided to segregate these patients for more intensive therapy. The possibility that T-ALL was demonstrated. Patients with >40% E-rosette-forming marrow blasts at 4°C were considered unequivocally to have T-ALL. Patients with 20%–40% marrow blasts with E-receptor positivity at 4°C (intermediate positivity) could be registered on the study only if they had prior chemotherapy had been administered. (3) Bone marrow contained >25% lymphoblasts. (4) E-rosette-defined T-ALL was demonstrated. Patients with >40% E-rosette-forming marrow blasts at 4°C were considered unequivocally to have T-ALL. Patients with 20%–40% marrow blasts with E-receptor positivity at 4°C (intermediate positivity) could be registered on the study only if their overall clinical and laboratory findings at diagnosis were also suggestive of T-cell disease. Patients with <20% E-rosette-forming marrow blasts at 4°C were not eligible for the study.

**Children with T-cell acute lymphocytic leukemia (T-ALL) have a poorer prognosis than children with non-T, non-B acute lymphocytic leukemia (ALL).** Treatment programs, which have proven highly effective for the majority of children with ALL, have produced significantly shorter durations of remission for pediatric patients with T-ALL.\(^1\)\(^-\)\(^11\)

**MATERIALS AND METHODS**

**Patients**

Patients ≤18 yr of age at diagnosis were eligible for the study if the following conditions were met: (1) Informed consent of parents and of older patients was obtained in accordance with institutional guidelines. (2) No prior chemotherapy had been administered. (3) Bone marrow contained >25% lymphoblasts. (4) E-rosette-defined T-ALL was demonstrated. Patients with >40% E-rosette-forming marrow blasts at 4°C were considered unequivocally to have T-ALL. Patients with 20%–40% marrow blasts with E-receptor positivity at 4°C (intermediate positivity) could be registered on the study only if their overall clinical and laboratory findings at diagnosis were also suggestive of T-cell disease. Patients with <20% E-rosette-forming marrow blasts at 4°C were not eligible for the study.

*From the University of Mississippi Medical Center; M.D. Anderson Hospital; Duke University Medical Center; University of Florida JHM Health Center; University of Oklahoma Health Sciences Center; Baylor College of Medicine; Washington University Medical Center; Cleveland Clinic Foundation; University of Kansas Medical Center; and University of New Mexico School of Medicine.*

**Supported in part by the following grants awarded by the National Cancer Institute, DHEW: CA-15989, CA-03713, CA-15525, CA-29139, CA-11233, CA-03161, CA-05587, CA-26756, CA-28841, and CA-20699.**

**Submitted January 30, 1982; accepted June 23, 1982.**

Address reprint requests to D. Jeanette Pullen, M.D. (POG #7615), Pediatric Oncology Group, Operations Office, 4386 Lindell Boulevard, St. Louis, MO 63108.

© 1982 by Grune & Stratton, Inc.

0006–4971/82/6005–0015$02.00/0
**Techniques**

Bone marrow samples were stained by routine methods using Wright-Giemsa, Sudan black B or peroxidase, and acid phosphatase stains. Patients with blasts showing Sudan black B or peroxidase positivity were ineligible for the study.

Mononuclear white cells were separated from pretreatment heparinized bone marrow samples using Ficoll/Hyppaque gradient centrifugation. These cells were tested for receptors for sheep erythrocytes using the same protocol at each institution. All patients had E-rosette determinations performed on marrow samples at 4°C. Most of the patients had E-rosettes after incubation at 37°C to determine whether the E-rosettes showed stability with incubation. Heat lability was defined as a decrease in E-rosette positivity from ≥40% at 4°C to <20% at 37°C. The protocol stipulated that the morphology of rosetting cells be examined by cytocentrifuge technique to document the cells as blasts.

Quality control for the E-rosette determinations was assured by requiring that each institution, before entering patients on the study, evaluate the percentage and absolute number of E-rosette-positive mononuclear cells in the peripheral blood of 10 healthy adults. The results were reviewed by the University of Oklahoma immunology reference laboratory personnel to determine that each institution’s results fell within the mean and standard deviation of the reference laboratory.

**Treatment**

The SWOG 7615 chemotherapy regimen shown in Fig. 1 is a modification of the LSA2-L2 NHL protocol, the details of which have been reported previously by Wollner. An absolute peripheral blood granulocyte count of 1000/µl was required in the current study before initiation of each course and/or cycle of chemotherapy, excluding the initial cyclophosphamide. Changes from the original protocol are described below.

**Induction.** The induction regimen was delivered as originally described except for the following changes: for patients with high (>50,000/µl) white blood cell counts (WBC), marked lymphadenopathy, marked hepatosplenomegaly, or high uric acid levels, the cyclophosphamide (CP) could be delayed and given between days 2 and 5, rather than on day 1. If cyclophosphamide was delayed, prednisone was begun on day 1 and vincristine on day 1 or day 2. This more gradual initiation of chemotherapy, as well as the use of high volume intravenous fluids, alkalinization, and allopurinol, was utilized in an attempt to prevent metabolic changes of rapid cell lysis. Daunorubicin was delayed until the third week of induction therapy, if necessary, in order to achieve a granulocyte count of ≥1000/µl prior to administration of daunorubicin.

**Consolidation.** The cytosine arabinoside (ARA-C)–thioguanine (TG) courses in consolidation were modified by reducing the ARA-C dosage to 100 mg/sq m/day for each 5-day course and the TG to 50 mg/sq m/dose. A fourth ARA-C/TG consolidation course was given if the absolute granulocyte count (AGC) was >1000/µl after the third ARA-C/TG course. L-Asparaginase dosage was reduced to 6000 U/sq m daily and was given daily for 14 consecutive days.

**Maintenance.** The 5 cycles of each consecutive course of maintenance therapy were given as originally described. After the maximum daunorubicin (DNR) dose was reached, BCNU (60 mg/sq m i.v. on day 1; vincristine (VCR) 2 mg/sq m max 2 mg i.v. weekly for 4 doses beginning on day 3 or 4; prednisone (PRED) 60 mg/sq m (max 60 mg) p.o. beginning with VCR and continuing for 28 days with 7 days decremental dosage; methotrexate (MTX) 6.25 mg/sq m i.v. on day 1; thio-
LSA₂-L₂ THERAPY FOR T-CELL LEUKEMIA

mg/sq m) was substituted for DNR in maintenance cycle 2 and CP (600 mg/sq m) was substituted for BCNU in maintenance cycle 3. Maximum DNR cumulative dose was 500 mg/sq m except for those patients who had received mediastinal irradiation. For the latter group maximum DNR dose was 350 mg/sq m.

Central nervous system (CNS) prophylaxis. Intrathecal (i.t.) methotrexate (MTX) was used for CNS prophylaxis and was administered as described by Wollner using a 6.25 mg/sq m dose.¹⁴,¹⁷

CNS disease treatment. Patients with CNS leukemia at the time of diagnosis received treatment to the CNS according to the SWOG 7308 CNS no. 5 or SWOG 7712 CNS no. 6 studies. In the CNS no. 5 study, triple i.t. medications were given twice weekly until complete remission (CR) was obtained, then at increasing intervals of 2, 4, 6 and 8 wk for 4 injections, then every 8 wk throughout the duration of systemic maintenance therapy. The CNS no. 6 study utilized triple i.t. medications weekly for 6 wk for induction of CNS remission. Patients were then randomized to receive either cranial irradiation plus i.t. medications every 5 wk throughout maintenance or craniospinal irradiation without further chemotherapy. Dosages of i.t. medications were: MTX 15 mg/sq m (maximum 15 mg); hydrocortisone 15 mg/sq m (maximum 15 mg); and ARA-C 30 mg/sq m (maximum 30 mg). When i.t. chemotherapy was given, leucovorin was administered intramuscularly or orally to reduce the systemic side effect of MTX marrow suppression.

Mediastinal irradiation. The 7615 protocol initially suggested that radiotherapy (3000 rad) be administered to the mediastinum for patients presenting with a mediastinal mass. Shortly after the protocol was opened to patients with T-ALL, it was amended to state that mediastinal irradiation would be used only for those patients with x-ray evidence of a mediastinal mass persisting after the induction phase of chemotherapy or for those requiring mediastinal irradiation as an emergency measure at the time of diagnosis. This amendment was introduced for the following reasons. (1) There was concern that mediastinal irradiation administered to patients with T-ALL during induction might cause severe marrow depression, thus delaying initiation of the consolidation portion of the protocol. (2) By avoiding irradiation to the mediastinum, the risk of daunorubicin-induced cardiomyopathy could be lessened and a higher maximum cumulative dose of daunorubicin could be delivered during maintenance.

Definitions of Treatment Response

Complete remission (CR) was defined as less than 5% bone marrow blasts and no evidence of extramedullary leukemia. CNS relapse was defined as greater than 10 mononuclear cells per microliter CSF, with blasts demonstrated on cytospin. A patient was taken off study if marrow relapse or extramedullary relapse occurred. Treatment was stopped after 3 yr in complete CR. Testicular biopsies were obtained on males prior to stopping chemotherapy at 3 yr.

Statistics

The method of Kaplan and Meier was used to construct the life tables and curves,¹⁸ and the standard errors of these estimates were computed using the techniques described by Peto et al.¹⁹ The Cox life table regression model under the proportional hazard assumption was used in the analysis of prognostic factors.²⁰ Graphical methods were used to investigate the proportional hazard assumption. The Mantel-Haenszel statistic (log rank) was also used to compare life tables.²¹ If expected cell frequencies permitted, contingency tables were analyzed using the classical chi-square statistic. Otherwise, an exact procedure based on the chi-square statistic was used.²²

RESULTS

Patient Characteristics

Sixty patients were registered on the T-cell leukemia portion of the POG 7615 study. Fifty-three of these patients were eligible for the study, but 7 were ineligible for the following reasons. Three patients had E-rosette determinations performed only on peripheral blood samples. Three patients had tissue biopsies showing "convoluted cell" histology but had no marrow E-rosette studies. One patient had no records submitted for review.

The presenting clinical and laboratory characteristics of the 53 eligible patients are summarized in Table 1. The WBC, hemoglobin, and platelet count values represent results obtained prior to transfusion of any blood product and prior to the initiation of chemotherapy. All 53 patients had greater than 50% blasts in the bone marrow differential counts, and 46/53 had greater than 70% marrow blasts. Forty-two of 53 or 79% of the patients had >40% marrow blasts that formed E-rosettes at 4°C. The remaining 11 patients (21%) had 20–40% of blasts that formed E-rosettes.

<p>| Table 1. Clinical and Laboratory Characteristics at Diagnosis |
| POG 7615 T-Cell Leukemia Patients |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total eligible patients</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>42</td>
<td>79</td>
</tr>
<tr>
<td>Females</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>41</td>
<td>77</td>
</tr>
<tr>
<td>Black</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Latin American</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Age (median 10 yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5 yr</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>6–10 yr</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>≥11 yr</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>WBC 1.0 x 10³ (median 75.6 x 10³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10.0</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>10.0–50.0</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>50.0–100.0</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>&gt;100.0</td>
<td>22</td>
<td>42</td>
</tr>
<tr>
<td>Hemoglobin (median 10.9 g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9 g/dl</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>≥9 g/dl</td>
<td>37</td>
<td>70</td>
</tr>
<tr>
<td>Platelet count 1.0 x 10⁹ (median 47.0 x 10⁹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50.0</td>
<td>26</td>
<td>49</td>
</tr>
<tr>
<td>50.0–100.0</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>&gt;100.0</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>Uric acid (median 10 mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8.0 mg/dl</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>≥8.0 mg/dl</td>
<td>35</td>
<td>67</td>
</tr>
<tr>
<td>Other findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>CNS disease</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Nodes &gt;2 cm</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td>Hepatomegaly &gt;5 cm</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>Splenomegaly &gt;5 cm</td>
<td>39</td>
<td>74</td>
</tr>
</tbody>
</table>

From www.bloodjournal.org by guest on October 30, 2017. For personal use only.
at 4°C. Thirty of the 53 patients had E-receptor testing of marrow samples at 37°C as well as at 4°C. Three patients were demonstrated to have blasts with heat-labile E-receptors.

Response to Therapy

Since one patient was lost to follow-up during induction, 52 of the 53 patients were evaluable for response to induction therapy. Fortysix of the 52 evaluable patients, or 88%, attained CR. Two patients failed to attain CR, although they completed the full course of induction chemotherapy. There were 4 deaths during induction. The deaths occurred on days 12, 13, 18, and 22 from the start of induction therapy. Death was attributed to infection and hemorrhage in 3 of the 4 patients and to infection alone in the fourth patient. Three of the four patients had absolute granulocyte counts <500/μl at the time of death and all four patients had severe thrombocytopenia.

The 46 patients who entered CR are evaluable for duration of continuous CR. One patient refused consolidation therapy after achieving CR. One patient died in CR at 12 mo after bilateral mastoiditis and cerebral arterial thrombosis. Two patients were lost to follow-up in CR, one at 5 mo and the other at 25 mo.

Figure 2 shows the Kaplan-Meier life table and plot for time to first treatment failure for the 53 eligible patients beginning with day 1 of induction therapy. Treatment failure is defined as induction failure, initial relapse at any site, death during induction, or death during initial CR. These data estimate with a standard error (SE) of 8.3%, that 40% of T-ALL patients on this therapy will demonstrate no type of treatment failure by 3 yr.

Fifty percent of the patients who attained CR developed either extramedullary or marrow relapse by 13 mo. However, only one patient has thus far developed an initial relapse occurring later than the 16th month of maintenance therapy. The range of follow-up for patients remaining in CR at all sites is 24–49 mo, with a median duration of follow-up of 39 mo. Kaplan Meier life table analysis of the duration of continuous CR estimates, with a SE of 9%, that 46% of patients who achieved CR will remain in CR at all sites by 3 yr. A plot of this life table would be similar in shape to the curve in Fig. 2.

Thus far, 11 patients have had therapy discontinued after 3 yr in continuous CR. One patient has relapsed after discontinuing therapy. The other 10 patients currently remain in CR with a median follow-up off therapy of 8 + mo. Two patients in continuous CR had therapy discontinued prior to 3 yr, one at 18 mo because of chronic osteomyelitis and the other at 27 mo because of chronic fungal meningitis. These 2 patients...
currently remain in CR at 11+ and 12+ mo, respectively, after stopping therapy. Nine of the 13 patients who have had chemotherapy discontinued while in CR are boys. All 9 of the boys had negative testicular biopsies at the time therapy was discontinued.

**Types of Relapse**

Details concerning the initial sites of relapse for the 24 patients who have developed either marrow or extramedullary relapses are as follows. Nine patients had isolated marrow relapse. Isolated CNS relapse occurred in 7 patients. Three patients had simultaneous marrow and CNS relapses. One patient had isolated mediastinal relapse and one had simultaneous marrow and mediastinal relapse. One patient had an isolated nodal relapse, while an additional patient had concurrent nodal and testicular relapses. The only patient who has demonstrated initial treatment failure occurring beyond 16 mo is a boy who developed combined marrow and testicular relapse at 38 mo, i.e., 2 mo after stopping therapy.

**CNS Disease**

Eight patients had documented CNS leukemia at the time of initial diagnosis. One of these patients died during induction. In the remaining 7 patients, CNS, as well as marrow, remission was attained. Three of these patients remain in continuous CNS and marrow remission at 24, 31, and 33 mo, respectively. These three patients received triple i.t. medications for induction and maintenance of CNS remission and one of the three also received cranial irradiation. As previously noted, isolated CNS relapse occurred in 7 patients. None of these 7 patients had documented CNS leukemia at the time of diagnosis.

**Mediastinal Disease**

Mediastinal radiation therapy was administered to only 6 of the 28 patients who had a mediastinal mass at the time of diagnosis. These 6 patients received mediastinal irradiation prior to the time the protocol was amended. One of these patients required mediastinal irradiation as an initial emergency measure. Of these 6 patients, 5 have developed relapses. None of the 6 patients developed a mediastinal relapse.

Twenty-two of the 28 patients with mediastinal mass at diagnosis did not receive radiation therapy to the mediastinum. Three of these 22 patients expired during induction from infection and hemorrhage. Nineteen of these 22 patients achieved CR; none showed x-ray evidence of residual mediastinal disease after completing induction chemotherapy. None of these 19 developed an isolated mediastinal relapse; 1 of the 19 developed simultaneous marrow and mediastinal relapses. Eleven of the 19 are in continuous CR at greater than 24 mo. There is no significant difference in duration of continuous CR between the 6 patients who had mediastinal irradiation and the 19 patients who did not ($p < 0.1$).

The only patient developing an isolated mediastinal relapse was a child who had not demonstrated a mediastinal mass on x-ray at the time of diagnosis. This child developed mediastinal relapse after 11 mo of CR.

**Survival**

Kaplan-Meier life table analysis of survival data for the 53 patients with T-ALL estimates that 48% (SE 8%) of patients will be alive 3 yr from diagnosis. Most patients who developed marrow relapse did not survive more than 7 mo after marrow relapse. However, 3 of the 7 patients who developed isolated CNS relapse are now surviving at greater than 44 mo from diagnosis.

**Prognostic Factors**

Clinical findings at diagnosis (Table 1) were analyzed to determine whether they influenced treatment response in patients with T-ALL. The following variables were examined: age, sex, race, white blood cell count (WBC), platelet count, hemoglobin (Hb) level, uric acid level, presence or absence of mediastinal mass, and the percentage of blasts forming E-rosettes at 4°C.

Cox's life table regression model was used as a stepwise procedure to identify the most important presenting findings at diagnosis as related to the dependent variable “time to first treatment failure from day 1 of induction therapy.” Hb level, platelet count, uric acid level, race, and the presence or absence of a mediastinal mass were not statistically significant at any step of the analysis. WBC was entered into the single parameter model as a continuous variable in two ways: first, as the actual WBC and then as the natural logarithm ($\ln$) of the WBC. WBC was not significant ($p = 0.08$) but $\ln$ (WBC) was significant ($p = 0.01$). However, as a dichotomous variable, WBC $\geq 50,000/\mu l$ was statistically significant at the 0.002 level. Age $> 10$ yr and male sex were also statistically significant predictors of prognosis. The significance levels demonstrate that the dichotomous variable, WBC, is the most important of the variables.

Although the percentage of marrow blasts forming E-rosettes (E) at 4°C ($\geq 40$% E versus $< 40$% E) was not in itself significantly related to time to treatment failure, it was significant in a model that included WBC. After adjusting for the effect of WBC, patients with $< 40$% E at diagnosis have a poorer prognosis than those with $> 40$% E. Since this apparent difference is
possibly due to biased selection of patients within the 20%-40% E-defined T-ALL subgroup (see eligibility criteria), this factor was excluded from subsequent analyses.

No statistical evidence related the presence of a mediastinal mass to WBC (p < 0.2). Males were more likely to present with WBC ≥ 50,000/μl (p = 0.05), and in a model adjusting for WBC, sex was no longer significantly related to outcome. There is no evidence that age at diagnosis is related to WBC. Within the subgroup of patients with WBC ≥ 50,000/μl, age is not important in predicting prognosis. However, in the group of patients with WBC < 50,000/μl, patients > 10 yr of age at diagnosis fare worse than those < 10 yr of age (Mantel-Haenszel test, p < 0.01). The Kaplan-Meier estimates of the proportion in these latter two groups experiencing no failure 3 yr after diagnosis are 34% (SE 16%) and 86% (SE 11%), respectively.

In summary, WBC greater or less than 50,000/μl was the single most important prognostic factor in this T-ALL study. Using the proportional hazard’s assumption, the Cox life table regression model estimates the chance of failure on a given day to be 3.36 times as great for a patient with presenting WBC ≥ 50,000/μl as for a patient with WBC < 50,000/μl. A 95% confidence interval for the instantaneous relative risk is (1.52, 7.42). Figure 3 demonstrates that the probability of developing initial treatment failure for the 29 patients with WBC ≥ 50,000/μl at diagnosis is significantly greater than for the 24 patients with presenting WBC < 50,000/μl (p < 0.01 by log rank test). Figure 3 estimates that only 19% (SE 8%) of the higher risk group will be failure-free at 3 yr as compared to 67% (SE 11%) of the lower risk group.

There was no significant difference in the occurrence of CNS involvement at diagnosis between the lower WBC group (2 of 24 patients) and the higher WBC group (5 of 27 patients). We asked whether the higher treatment failure rate in the ≥ 50,000/μl WBC group could be explained completely by a higher incidence of isolated CNS relapse in that group. Analysis showed that the ≥ 50,000/μl WBC group does have a shorter time to isolated CNS relapse than the < 50,000/μl WBC group (p = 0.054). However, if CNS relapse is eliminated from the analysis (failure defined as death or any relapse other than CNS), the ≥ 50,000/μl WBC group still has a significantly shorter CR duration than the < 50,000/μl WBC group (p < 0.01).

Heat lability of E-receptors could not be analyzed for possible prognostic significance because there were too few patients with blasts showing this characteristic. Of the 3 patients who had blasts showing E-receptor heat lability, 2 remained in CR at all sites at 31 + and 47 + mo, respectively, and one was lost to follow-up in CR at 5 mo.

**Toxicity and Protocol Delivery**

The toxicity of the original LSA2-L2 protocol has been previously described. Considerable toxicity was encountered with the POG 7615 modified LSA2-L2 regimen, with myelosuppression being the most frequently encountered toxicity during the induction, consolidation, and maintenance phases of the protocol. Thirty percent of the patients developed severe (absolute granulocyte count 250/μl–500/μl) or life-threatening (absolute granulocyte count < 250/μl) neutropenia at one or more times during treatment. The 4 deaths during induction were directly related to myelosuppression. Most patients had delays in initiating a subsequent course of maintenance therapy because of neutropenia and/or thrombocytopenia persisting from...
the previous 5-day maintenance course. Individual adjustments in drug dosages were often necessary during maintenance.

Metabolic problems were encountered, secondary to the rapid lysis of leukemic cells, during the first few days of induction therapy. The majority of patients had very high WBCs and/or marked lymphadenopathy or hepatosplenomegaly at diagnosis (Table 1). Even with the gradual initiation of chemotherapy in patients with high leukemic cell burden, along with the prescribed use of high fluids, alkalinization, and allopurinol, 7 patients developed nephropathies and 1 of these 7 patients required dialysis. The patients with nephropathies demonstrated BUNs in the 30-100 mg/dl range, mild to moderate elevations of serum creatinine, hypocalcemia, hyperphosphatemia, and hyperkalemia. Four patients developed tetany. Uric acid levels were normal in some patients at the time of maximal BUN elevation, suggesting xanthine nephropathy secondary to allopurinol control of uric acid build-up.23

The mean and median times required to complete induction were 4.9 wk and 5.0 wk, respectively. Three patients required greater than 2 wk, but less than 3 wk, rest period for marrow recovery between completion of induction and initiation of consolidation. Consolidation required mean and median times of 9.0 wk (from day 1 of consolidation to the day BCNU was given). Six patients required a greater than 2 wk, but less than 3.5 wk, rest period between completion of consolidation and initiation of maintenance. The mean and median times required to complete a 5-cycle course of maintenance chemotherapy were 11 wk.

During consolidation, 68% of the patients received all 4 cycles of cytosine arabinoside/thioguanine, while 86% received at least 3 cycles. Ninety-one percent of the patients received at least 12 doses of L-asparaginase. The maintenance data were analyzed to determine what proportion of patients received ≥75% of the specified dosages for each of the 5 cycles in all courses. Results were as follows: thioguanine/cyclophosphamide, 75%; hydroxyurea/daunorubicin, 56%; methotrexate/bis-nitrosurea, 81%; cytosine arabinoside/vincristine, 78%; and methotrexate i.t., 100%.

Although the schedule of the LSA2-L2 protocol is a complicated one, all of the patients were able to receive most of their maintenance chemotherapy as outpatients, though frequent return visits to the clinic were required. Most of the children were able to attend school and pursue normal activities.

**DISCUSSION**

T-ALL accounts for only 10%-15% of the cases of ALL in childhood.11,24-28 Therefore, the 53 children with E+ T-ALL described in this report constitute a relatively large group of pediatric T-ALL patients. Certain presenting findings are now well recognized as occurring with significantly higher frequency in children with T-ALL than in those with non-T-ALL. These include: mediastinal mass, median age of 10-12 yr, decided male predominance, high WBC, and high hemoglobin.6,9,11,25-30 The patients in the present series demonstrated these expected characteristics.

Laboratory evidence for the diagnosis of T-ALL in the current report was obtained solely from E-receptor testing of marrow samples. Therefore, this report does not address the more recently recognized, still smaller group of patients with T-antigen-positive (T+), E-negative (E-) T-ALL.9,13,26-28,31-35

Comparison of treatment results among reported series of T-ALL patients is hampered by the fact that criteria have varied as to the degree of E positivity used to distinguish T-ALL.1,9 In addition, more recent reports have utilized membrane antigen testing with anti-T sera of varying specificities to define T-ALL, and may or may not have analyzed separately the small group of T+, E- patients as to treatment response.9,11,26,28,32,35

Our study's remission induction rate was 88%. Several earlier studies, using less intensive induction regimens, demonstrated CR rates of 90%-100%.4,6,8 Two more recent reports showed CR rates of 69% and 84%, respectively.11,35 Although the latter two studies showed diminished CR frequency in T-ALL as compared to non-T-ALL, the major problem in T-ALL appears to be maintaining, rather than inducing, remission.

Even though intensive induction therapy may not be required in order to obtain CR in T-ALL, it may be important in influencing duration of remission. A central premise of Dr. Wollner's LSA2-L2 protocol for NHL was that fast and maximum decrease in all bulky disease is a necessity for long-term CR.16 Our study's delay of cyclophosphamide administration from day 1 to days 2-5 of induction departed somewhat from the intent of the original protocol, but seemed necessary in T-ALL patients with high leukemic cell burden in order to lessen the risk of severe metabolic problems due to cell lysis.

This report projects for T-ALL patients at 3 yr from diagnosis a 40% overall failure-free rate and a 46% continuous CR rate for patients who attained CR. Although the median failure-free duration in our study is just 13 mo, only one patient has developed relapse later than 16 mo. These results represent a marked improvement over earlier reports of small numbers of patients with T-ALL (8-20 patients), in which most patients had relapsed by 5-12 mo.2,9 The results also appear superior to those recently reported by Greaves
et al. for 43 major subset (T', E', Ia', cALL') T-ALL patients pooled from various treatment regimens of the UKALL studies.11

Children with T-ALL have been previously reported to have a higher incidence of CNS involvement at diagnosis and a higher incidence of CNS relapse than children with non-T-ALL.489' The results of the current study confirm these observations. The CNS prophylaxis utilized in this protocol was inadequate for preventing CNS relapse as evidenced by the fact that CNS relapse accounted for 29% of the initial relapses in the series and for 7 of the 10 extramedullary relapses. Because of these results, the subsequent POG T-ALL protocol (POG 7837) is employing more intensive CNS prophylaxis, using cranial radiation plus triple-medications intrathecal chemotherapy throughout maintenance in the modified LSA2-L2 treatment arm.

Besides an increased frequency of CNS relapse, T-ALL has also been associated with a high frequency of early extramedullary relapse at other sites, especially the testes.9,36 Only 2 of the 42 boys in this study developed testicular relapse, which suggests that the modified LSA2-L2 regimen is a relatively effective one for preventing testicular relapse in boys with T-ALL.

Jereb has recently analyzed the role of local radiation in children with NHL treated with the LSA2-L2 protocol at the Memorial Sloan-Kettering Cancer Center through 1973. Radiation therapy to bulk disease in patients with primary tumors of various sites did not improve patient survival rate significantly but did appear to prevent local recurrence. Jereb's report included 9 patients who had a mediastinal mass at the time of diagnosis.37 The results of our study suggest that for patients with T-ALL, who have a mediastinal mass at presentation, there is no advantage to mediastinal irradiation, either from the standpoint of lengthening duration of CR at all sites, or from the standpoint of preventing local recurrence.

All patients in this T-ALL study were treated with the same chemotherapy regimen, regardless of clinical risk factors. This provides the distinct advantage of permitting comparison of prognostic factors among identically treated T-ALL clinical subgroups. However, direct comparison of response between T-ALL and non-T-ALL patients is impossible, since non-T-ALL patients were not treated simultaneously with the same regimen.

Mediastinal mass at diagnosis in ALL is associated with a high failure rate.3,13,36,38 This has been shown to be due to the almost exclusive association of mediastinal mass with T-ALL.3,9,11,28 It is interesting that within the group of T-ALL patients in this report, mediastinal mass was not significantly related to outcome, nor was it related to WBC. Greaves has also recently reported no correlation between mediastinal mass and WBC within the T-ALL patients in the UKALL series.11

Two previous reports have suggested that girls with T-ALL have a better prognosis than boys.33,39 In our study, sex was not a significant factor in outcome after adjusting for WBC. Greaves' results also showed no advantage for girls with T-ALL.11

Heat lability of E-rosettes has been previously reported by POG investigators as a possibly favorable prognostic finding for T-ALL patients.40,41 Although 2 of the 3 patients who had heat-labile E-rosettes in this study are in long-term CR, the number of such patients in this series is too small for statistical analysis.

The most important prognostic determinant in this T-ALL study proved to be the presenting WBC, as evidenced by a projected 3-yr failure-free rate of 19% in the higher WBC group compared to 67% in the lower WBC group. Most previous reports concerning T-ALL have contained too few patients to permit analysis as to whether outcome related to WBC within the T-ALL group.2,9 Recent reports by Greaves at al.11 and by Bowman35 have suggested, as does our study, that remission duration for T-ALL patients is strongly associated with WBC at presentation.

The \(\geq 50,000/\mu l\) WBC T-ALL subgroup in our study is faring poorly, with approximately the same long-term CR rate as that reported by others for high-risk (WBC defined) ALL subgroups from which patients with T-ALL were not excluded.42-44 Using the L2 protocol,44,46 which our modified LSA2-L2 regimen closely resembles, Haghibin reported long-term CR for only 3 of 13 high-risk (WBC >50,000/\mu l) ALL patients, with T-ALL patients not identified.44 Thus, our results indicate that, at least for the high WBC subgroup of T-ALL patients, treatment with a regimen successful for mediastinal lymphoma has not improved long-term treatment outcome over that obtained for high WBC, composite groups using other regimens.

The <50,000/\mu l WBC subgroup of T-ALL patients in this study is doing quite well. Since previous T-ALL reports have not analyzed outcome as related to WBC, there are very few data available for comparison of our results with others' for this subgroup. For St. Jude Total Therapy IX patients with WBC <25,000/\mu l, Bowman recently reported 6 (67%) of 9 patients with E' T-ALL to have relapsed.35 Greaves's report showed that 11 of 18 major subset (T', E', Ia', cALL') T-ALL patients with presenting WBC <100,000/\mu l either failed induction or had relapsed.11 Although the numbers are quite small and the WBC subgroups somewhat differently defined, it appears that our <50,000/\mu l WBC subgroup of E' T-ALL patients is faring better than has been reported for the lower WBC subgroups in two other studies.
Comparing results in this study with POG results using the same regimen in mediastinal non-Hodgkin's lymphoma (NHL), it appears that the T-ALL patients with <50,000/μl WBC at diagnosis have approximately the same long-term CR rate as do mediastinal NHL patients. This perhaps suggests that the lower WBC T-ALL patients are more clinically similar to the T-NHL than are the higher WBC T-ALL patients. However, in both the higher and lower WBC subgroups of T-ALL patients, relapses have been confined almost exclusively to the first 16 mo of therapy, suggesting a time at risk for both subgroups similar to that reported for patients with mediastinal NHL using the LSA2-L2 regimen.17,47,48

There has been much recent discussion as to whether T-ALL implies a poor prognosis independently of its high association with poor-risk clinical features, especially WBC.9,11,34,35,42 A more important question would appear to be whether there are biologic differences in T-ALL that necessitate that therapeutic regimens be designed differently for T-ALL patients and non-T-ALL patients with equivalent WBCs, in order to achieve maximum effectiveness for each group. There is already some data to suggest that different patterns of drug sensitivities may be found in T-ALL and non-T-ALL.49,50 Also, differing transit and homing patterns of T lymphoblasts may necessitate more intensive treatment of extramedullary sites in T-ALL than in non-T-ALL. Greaves's data showed that, even after adjusting for WBC, the incidence of CNS involvement was significantly higher in T-ALL than in non-T-ALL.11

The hypothesis of the present study was that therapy effective for T-NHL might prove efficacious for T-ALL. The modified LSA2-L2 regimen has afforded better overall results in T-ALL than previous reports have demonstrated. However, the remission duration is strongly associated with presenting WBC. The following problems are among those that need to be addressed in planning future treatment regimens for children with T-ALL: the high incidence of treatment failure within the first 13 mo of therapy, the need for more effective CNS prophylaxis, and the disproportionately high failure rate for patients who have WBC ≥50,000/μl at the time of diagnosis.

REFERENCES


Modified LSA2-L2 treatment in 53 children with E-rosette-positive T-cell leukemia: results and prognostic factors (a Pediatric Oncology Group Study)

DJ Pullen, MP Sullivan, JM Falletta, JM Boyett, GB Humphrey, KA Starling, VJ Land, PG Dyment, T Vats and MH Duncan