Adolescent and Adult Acute Lymphoblastic Leukemia: Prognostic Features and Outcome of Therapy. A Study of 293 Patients

By Michele Baccarani, Giovanna Corbelli, Sergio Amadori, Alice Drenthe-Schonk, Roel Willemze, Giovanna Meloni, Paul Lopes Cardozo, Clemens Haanen, Franco Mandelli, and Sante Tura

The case histories of 293 adolescent and adult patients with acute lymphoblastic leukemia (ALL) first seen and treated between 1969 and 1979 are reviewed. A complete remission (CR) was achieved in 79% of cases. Male sex, advanced age (>30 yr old), and early CNS involvement were the major determinants of remission failure. Median duration of first CR was 16 mo, with 23 patients (actuarial proportion 25%) alive and relapse-free at 5 yr. The major determinant of first CR length was white blood cell (WBC) count (best cut-off value at 35 × 10^9/liter). First CR length was also negatively affected by early CNS involvement, morphological FAB L3 subtype, and B-cell (SmIg+) leukemia, but these features were significantly associated with a high WBC count. First CR length in patients 11–15 yr old did not differ significantly from that of patients 16–59 yr old. The negative prognostic value of T-cell (E+) leukemia was not confirmed in this adult series. CNS prophylaxis provided an effective protection against CNS relapse. Maintenance chemotherapy was apparently more effective when 4 or more than 4 drugs were employed. "Low risk" patients (WBC count <35 × 10^9/liter still relapsed rather frequently (32% at 1 yr, 49% at 2 yr), with 33% of them alive and relapse-free at 5 yr. "High risk" patients (WBC count >35 × 10^9/liter ± early CNS involvement ± morphological L3 subtype ± B-cell leukemia) relapsed very quickly (50% at 6 mo, 70% at 1 yr), with only 6% of them relapse-free at 5 yr.

SURVIVAL in acute lymphoblastic leukemia (ALL) is to a large extent dependent on age, with the prognosis of children being better than that of adolescents and adults. In children, retrospective analysis of large series and prospective trials of therapy gave an important contribution to the knowledge of the disease and to treatment progress by making possible the distinction, and appropriate therapy of patients with different prognoses. Adolescents and adults received less frequent attention in spite of the fact that approximately 25% of all ALL occurs after the age of 11. More recently, several reports have drawn attention and renewed interest to adult ALL, but identification of prognostic features was not sharp, probably because the number of patients in each study was relatively small, and follow-up time was frequently shorter than needed. Thus, risk definition and prognosis of ALL in adolescents and adults was not clearly defined, and the management of the disease is still based on studies of childhood ALL. In an attempt to fill that gap, all patients more than 11 yr old who were admitted and treated at 4 hospitals over a 10-yr period were pooled and reviewed retrospectively for prognostic features and outcome of therapy.

MATERIALS AND METHODS

The study included 293 patients who were more than 11 yr old, previously untreated, first seen between 1969 and 1979 at the Division of Hematology at the University Hospitals of Roma (132 cases), Bologna (59 cases), Nijmegen (54 cases), and Leiden (48 cases). Some of these patients had been included in previous separate reports. The original diagnosis of ALL was based on cytologic examination of Giemsa-stained marrow and peripheral blood smears, and on peroxidase or Sudan black negativity.

Patients were analyzed for sex, age, mediastinum involvement, lymphadenomegaly, splenomegaly, hepatomegaly, proportion of blast cells in the marrow, Hb concentration, platelet count, WBC count, morphological FAB subtype, and morphological L3 subtype. Data on PAS reaction were available in 189 patients. Spontaneous E-rosette formation and surface membrane immunoglobulins (SmIg) were studied in 128 cases. Complete remission was defined by absence of clinical manifestations of leukemia, normal peripheral blood count, less than 5% blast cells in the marrow, and negative cytocentrifuge preparation of the cerebrospinal fluid.

Information on treatment included drug name, dose, and schedule of the agents that were employed for induction of complete remission (CR), CNS prophylaxis, maintenance chemotherapy, and therapy of first or subsequent relapses. In all hospitals, induction therapy was based on vincristine (VCR) (1.5–2.0 mg/sq m/wk × 4 to 6 wk) and prednisone (P) (40–60 mg/sq m/day × 4 to 6 wk), but many patients received also one or more other drugs, either because they were thought to need more aggressive treatment or because blast cells had not been cleared off after 3 or 4 wk of VCR and P. Thus, 98 patients (42%) were induced to CR by VCR and P alone, 28 patients by VCR, P, and l-asparaginase (ASP), 47 patients by VCR, P, and daunomycin (DAUNO), 32 patients by VCR, P, DAUNO, and cyclophosphamide (CYCLO), and 10 patients by all five drugs. The remaining 5 patients were induced to CR with different regimes, including arabinosyl-cytosine (ARA-C), 6-thioguanine (TG), and methotrexate (MTX).

Maintenance chemotherapy was based on 6-mercaptopurine...
of data on CR rate and length. Analytical data on survival are omitted, as they are a mere repetition of results which are presented in Table 1. Twenty-two patients (7.5%) failed to respond to prolonged and intensive antileukemic therapy (5–10 drugs), and died of leukemia 2–53 mo after diagnosis (median survival 6 mo). CNS leukemia was the only feature that was significantly related to induction failure. Thirty-nine patients (13.3%) died of infection, hemorrhage, or other less frequent complications (including liver, kidney, and heart failure) within 6 wk from admission, before completing induction chemotherapy. Death during induction was significantly more frequent in males than in females (34/181 or 19% versus 5/112 or 4%, p < 0.001) and in patients who were more than 30 yr old than in younger ones (26/115 or 23% versus 13/178 or 7%, p < 0.0005).

Life-table analysis of survival and relapse-free survival (first CR length), is shown in Fig. 1. Median values were 17 and 16 mo respectively. At 3 yr, 79 patients (actuarial proportion 31%) were alive, and 51 patients (actuarial proportion 31%) were relapse-free. At 5 yr, 31 patients (actuarial proportion 20%) were alive and 23 patients were relapse-free (actuarial proportion 25%).

Nine of 232 CR patients (4%) died of acute infection early during remission (within 2 mo). Another 7 patients (3%) died later on in continuous CR, 5–53 months after remission induction. The causes of death were infection (4 cases), hepatitis (1 case), liver cirrhosis (1 case), and encephalopathy (1 case).

Prognostic Features

Sex

Complete remission was achieved in 73% of 181 males and in 81% of 112 females. This difference was significant (chi-square 10.26, p < 0.005), and was caused by a higher death rate in males during remission induction. Interestingly, the difference was almost completely accounted for by the frequency of fatal infections: of 24 fatal infections, 23 occurred in males, and only 1 occurred in females. In contrast, sex difference influenced first CR length less significantly (chi square 3.48, p < 0.10).
Early CNS Involvement

CNS leukemia was shown at diagnosis in 11 patients and appeared early during remission induction (i.e., within 1 mo from diagnosis) in another 6 cases. Nine patients (53%) failed to achieve a CR, and all responders relapsed in 15 mo. Early CNS involvement occurred at any age, was more frequent in males (7%) than in females (3%), and was associated with a high initial WBC count, morphological L3 subtype, and B-cell (SmIg⁺) leukemia.

Age

Age was negatively related to CR rate and to first CR length. Adolescents (11–15 yr old) had the highest remission rate (91%), but did not differ significantly from young adults (16–29 yr old). Further analysis of young adults did not reveal any difference within that age group (e.g., CR rate was 83% in patients aged 16–19 and 81% in patients aged 20–29). In contrast, the CR rate of adult (30–59 yr old) and elderly patients (more than 60 yr old) was significantly lower (68% and 71%, respectively). Further analysis of adults (30–59 yr old) did not reveal any difference within that age group. Thus, the best cut-off point for relationship of age to CR rate was around the age of 30, with a \( p \) value of <0.005.

The relative relapse rate was lower in adolescents than in young adults and in young adults than in adults, but no significant difference could be found either between or within these age groups. Only the small group of elderly patients (≥60 yr old) had a slightly higher relative relapse rate (\( p < 0.05 \)).

WBC Count

WBC count was only slightly related to CR rate but had a very significant influence on first CR length (Table 2). Any count between 5 and 100 \( \times 10^9/\text{liter} \) allowed the division of the series into 2 groups that were significantly different, but the highest chi-square value was found with a cut-off at 35 \( \times 10^9/\text{liter} \) \( (p < 0.0005) \). Such a cut-off point was also evident by inspection of the relative relapse rate (Table 2) and was strengthened by lack of significance of the test for a trend among patients with a WBC count lower than 35 \( \times 10^9/\text{liter} \), as well as among patients with higher counts (Table 2). Relapse-free survival according to WBC count is shown in Fig. 2.

Morphological Subtype

The relationship of morphological FAB subtype to prognosis is shown in Table 3. CR rate was unaffected. The relative relapse rate was slightly higher in L2 than in L1 patients \( (p < 0.10) \) and in L3 patients than in the others \( (p < 0.05) \). L3 subtype was more frequent in males (7%) than in females (2%) and was significantly associated with a high WBC count (8 of 14 patients, or 57%, had a WBC count higher than 35 \( \times 10^9/\text{liter} \)).

Membrane Markers

The small group of patients with B-cell leukemia (SmIg⁺ blast cells) had the worst prognosis (Table 3). All of them relapsed within 16 mo. In contrast, patients with E⁺ blast cells fared exactly the same as patients with E SmIg⁻ leukemic cells.

Other Prognostic Features

Hb concentration, platelet count, PAS positivity of blast cells, splenomegaly, hepatomegaly, lymphadenomegaly, and the proportion of blast cells in the marrow had no relationship to prognosis.

Mediastinal involvement was recorded in 19 patients (6.5%), and 16 of them or 84% achieved CR.

<table>
<thead>
<tr>
<th>WBC ( \times 10^9/\text{Liter} )</th>
<th>No. of Patients</th>
<th>Complete Remission</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>&lt;2</td>
<td>22</td>
<td>19 (86%)</td>
<td>9</td>
</tr>
<tr>
<td>2–4.9</td>
<td>66</td>
<td>57 (86%)</td>
<td>31</td>
</tr>
<tr>
<td>5–9.9</td>
<td>39</td>
<td>33 (85%)</td>
<td>24</td>
</tr>
<tr>
<td>10–19.9</td>
<td>39</td>
<td>30 (77%)</td>
<td>19</td>
</tr>
<tr>
<td>20–34.9</td>
<td>31</td>
<td>23 (74%)</td>
<td>14</td>
</tr>
<tr>
<td>35–49.9</td>
<td>20</td>
<td>14 (70%)</td>
<td>12</td>
</tr>
<tr>
<td>50–99.9</td>
<td>27</td>
<td>18 (67%)</td>
<td>16</td>
</tr>
<tr>
<td>≥100</td>
<td>46</td>
<td>35 (76%)</td>
<td>30</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 7.83 \]
\[ p < 0.40 \]

\[ \chi^2 = 3.36 \]
\[ p < 0.10 \]

0. observed number of relapses; E, extent of exposure to risk of relapse; O/E = relative relapse rate.
The duration of CR of these patients was short (median 7 mo), and only 2 of them were relapse-free after 4 yr. However, the difference with mediastinum-negative patients was not significant (chi square 2.45, $p < 0.20$).

**Relapse**

Hematologic relapse terminated first CR in 76% of cases. Primary isolated nonhematologic relapse was rare and affected CNS (11 cases or 7%) or mediastinum (4 cases or 3%). In 23 cases (15%), a combined hematologic and nonhematologic relapse occurred, and this was more frequent in patients who had presented with an elevated WBC count. Testicular relapse was recorded in 10 of 97 male relapses (10%). CNS relapse occurred in 3 of 17 patients (18%) who had no CNS prophylaxis, in 11 of 118 patients (9%) who received cranial irradiation and i.t. chemotherapy, and in 7 of 95 patients (7%) who were given only i.t. chemotherapy. No relationship of CNS relapse to age could be shown.

Eighty-five of 157 relapsed patients (54%) were reinduced to CR, but duration of second remission (median 5.5 mo) and survival (median 7 mo) after relapse were rather short (Fig. 3).

**Table 3.** Relationship of Morphological FAB Subtype and Cell Membrane Markers to Complete Remission Rate and to Duration of First Complete Remission

<table>
<thead>
<tr>
<th>Morphological FAB Subtype</th>
<th>No. of Patients</th>
<th>Complete Remission</th>
<th>Relapse Rate</th>
<th>O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>45 (17%)</td>
<td>37 (82%)</td>
<td>21</td>
<td>30.3</td>
</tr>
<tr>
<td>L2</td>
<td>210 (78%)</td>
<td>168 (80%)</td>
<td>117</td>
<td>114.1</td>
</tr>
<tr>
<td>L3</td>
<td>14 (5%)</td>
<td>10 (71%)</td>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>L1 vs L2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 + L2 vs L3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membrane Marker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E Smlg</td>
<td>94 (73%)</td>
<td>76 (81%)</td>
<td>46</td>
<td>46.1</td>
</tr>
<tr>
<td>E'</td>
<td>25 (20%)</td>
<td>22 (87%)</td>
<td>14</td>
<td>13.8</td>
</tr>
<tr>
<td>Smlg'</td>
<td>9 (7%)</td>
<td>6 (67%)</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>E Smlg' vs E'</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E Smlg + E' vs Smlg'</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$O$, observed number of relapses; $E$, extent of exposure to risk of relapse; $O/E$, relative relapse rate.
Therapy of Remission Induction

The length of first CR was apparently unrelated to induction chemotherapy, either in the low or in the high WBC group. However, these results could be biased by nonrandom allocation of patients to treatment. In fact, many patients received one or more other drugs in addition to VCR and P, either because they were thought to need more aggressive treatment or because blast cells had not been cleared off after 3 or 4 wk of VCR and P.

Maintenance Chemotherapy

Seventeen of 232 patients (7%) received no maintenance chemotherapy, and 4 other patients were given only one drug. All these patients but 2 relapsed very quickly and will not be considered further on. Of the remaining 211 patients, 46 were given 2–3 drugs (6-MP daily and MTX weekly in 31 cases, 6-MP, MTX, and another drug in 15 cases), 63 were given 4 drugs (6-MP, MTX, and pulses of VCR and P), 58 were given 5 drugs, and 44 were given 6 or 7 drugs (always including 6-MP, MTX, VCR, and P). The other drugs were DAUNO (76 cases), ARA-C (38 cases), TG (25 cases), CYCLO (17 cases), ASP (5 cases), and a nitrosourea (3 cases). The duration of first CR (Fig. 4) was significantly shorter in patients who were maintained with 2 or 3 drugs than in patients who were maintained with 4–7 drugs. This was inde-
Long-Term Survivors were given 4, 5, 6, or 7 drugs, independent of initial WBC count:

BACCARANI ET AL.

Survivors had received CNS prophylaxis and all but one were in first continuous CR after more than 6 months of therapy for 10-90 mo (median 44 mo). Interestingly, 2 of 5 patients with FAB L3 cytotype, and 1 of 2 patients with Smlg blast cells were in first CR for more than 35 x 10^9/liter (31% versus 8%, p < 0.02), and from all adults aged below 60 as to CR duration. A worse prognosis, as compared to children less than 10 yr, was a WBC count for prognosis was situated between 10 and 50 x 10^9/liter, and p < 0.0005 for WBC < 35 x 10^9/liter. There was no difference among patients who had been induced to CR their disease at diagnosis was compared with the population at lowest risk of relapse. The features of this small group provided the best sample of a patients' features the number was too small to allow any calculation.

Although the curve did not form a true plateau, as 2 of 5 patients less than 30 yr old became long survivors, as age on prognosis depended much more on CR rate than remission duration, or both. Since treatment was variable and was not guided by a uniform protocol, it was impossible to appreciate how much the definition of remission induction (23/112 in males and 1/100 in females) but their influence on first CR length could not be properly evaluated as they were always associated to hematologic relapse. The relationship of young age to CR rate, but not to first remission rate, was found by Omura et al. and was also observed in adult ALL with some exceptions. This study provided unequivocal evidence in adolescents and adults that WBC count was always associated to hematologic relapse.

Table 4. Summary of Prognostic Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
<th>Rate</th>
<th>Length</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>62%</td>
<td>0.60 p</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Early CNS</td>
<td>5%</td>
<td>0.30 p</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>62%</td>
<td>0.60 p</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Smlg blast cells</td>
<td>7%</td>
<td>0.30 p</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>FAB L3 cytotype</td>
<td>5%</td>
<td>0.30 p</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>62%</td>
<td>0.60 p</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Early CNS</td>
<td>5%</td>
<td>0.30 p</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Smlg blast cells</td>
<td>7%</td>
<td>0.30 p</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

This study showed that prognosis of adolescent and adult ALL patients was dependent on 6 features (Table 4) that influenced either remission rate, or outcome of patients aged above 60, the probability of remaining in treatment.
The uncertainty on cut-off value(s) descended from the intrinsic difficulty of selecting one or more values out of a linear series of data such as WBC count. Any cut-off point may be arbitrary, and its accuracy for risk definition is a function of the number of patients being studied, as it was shown by analysis of a great number of children. Based on this series of 232 CR patients, we suggest that a WBC count of $35 \times 10^9$/liter may be a valuable cut-off point of prospective studies of adult ALL.

Another 3 features that occurred in a minority of the cases, contributed to the identification of smaller subgroups of patients with a significantly poorer prognosis (Table 4). Early CNS involvement (5% of cases), morphological FAB L3 subtype (5% of cases), and B-cell (SmIg+) leukemia (7% of typed cases) were significantly associated with each other and with a high WBC count. On the other hand, their number was too small to allow for further analysis according to the WBC count.

In this adult series, we could not confirm the negative prognostic value of mediastinal involvement and of T-cell (E+) leukemia as described in children. These results should be looked at with caution because of the relatively small number of cases involved (19 patients had a mediastinal mass and 25 patients had E+ blast cells). This may explain the lack of significance ($p < 0.20$) of the log rank test among patients with and without mediastinal involvement in spite of a median CR duration of 7 and 17 mo, respectively. The similarity of E+ and E- patients was more impressive ($p < 0.60$ for CR rate and $p < 0.95$ for first CR length), but it should not be overlooked that in adults a remarkable proportion, as high as 40%, of E- leukemias are "null" (cALL) leukemias and that "null" leukemia may have a worse prognosis. In this retrospective study, no data were available about cALL+ (common) and cALL- (null) subtypes, as well as about minor T subsets.

All the other clinical and laboratory features that were analyzed in this study had no proven influence on prognosis. There it was a borderline difference ($p < 0.10$) in first CR length between morphological FAB L1 and L2 subtypes. However, smears were reviewed separately in each hospital, and the classification may allow for a significant lack of concordance among different observers.

The relevance of different treatments to results of therapy could only be touched on, due to the retrospective character of the study, and to the different and mutable policies of therapy that were used in the 4 hospitals over a 10-yr period. It should be emphasized that we could not estimate the influence of induction chemotherapy on first CR length, as the number and type of drugs that were used for remission induction was dependent in part on the estimated risk and on the assessment of early response to therapy. Contrary to induction therapy, maintenance chemotherapy was not modeled according to the estimated risk. Patients who were systematically given four or more drugs (including always 6-MP, MTX, VCR, and P) fared significantly better than patients maintained with two or three drugs, and this was independent of WBC count at diagnosis. This information may be of value for planning future therapy of adult ALL. It is worth noting that childhood studies had suggested the contrary, i.e., that addition of other drugs to 6-MP and MTX offers no benefit.

CNS prophylaxis, given as soon as remission was achieved, provided an effective protection against CNS leukemia. Apparently, the result was independent of the modality (cranial irradiation plus i.t. drugs or i.t. chemotherapy alone), but the period of time to hematologic relapse was relatively short. When it will be possible to significantly prolong CR length, the relationship of the modality of CNS prophylaxis to results should be reevaluated, especially in patients presenting with a high WBC count. The same proviso may apply to the problem of testicular leukemia. At present, the main problem of males with an elevated WBC count is early marrow relapse, but in that group, 7 of 38 (18%) of hematologic relapses were accompanied by testicular relapse. In the future, the assessment of CR in male patients with a high WBC should probably include a biopsy of the testis.

In conclusion, advanced age (≥30 yr) and male sex were the major determinants of early failure, as they were associated with a higher death rate early during remission induction. This information is of value for comparative data analysis and emphasizes the need for better supportive therapy. The duration of first CR and the probability to achieve a cure were inversely affected by WBC count (>35 × 10^9/liter). Fifty percent of such patients relapsed in 6 mo, and 70% relapsed in 1 yr. Only 6% of them were alive and relapse-free at 5 yr. Analysis of relapse suggested that extramedullary leukemia could play an important role in terminating remission of these high-risk patients, especially those of male sex. These data provided unequivocal evidence that traditional treatment of high WBC count patients was absolutely unsatisfactory, thereby confirming that other drugs and other modalities of therapy have to be developed. In the "low-risk" group (WBC count <35 × 10^9/liter), 33% of patients were alive and relapse-free at 5 yr, indicating that although there is still a great need for improvement, standard treatment was not useless and less radical changes of therapy may be recommended.
REFERENCES


Adolescent and adult acute lymphoblastic leukemia: prognostic features and outcome of therapy. A study of 293 patients

M Baccarani, G Corbelli, S Amadori, A Drenthe-Schonk, R Willemze, G Meloni, PL Cardozo, C Haanen, F Mandelli and S Tura