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

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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) who relapsed early CNS involvement with morphological L3 subtype or 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 (289 cases), Hb concentration, platelet count (281 cases), WBC count (290 cases), and morphological FAB subtype (268 cases). 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 x 4 to 6 wk) and prednisone (P) (40–60 mg/sq m/day x 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 regimens, including arabinosyl-cytosine (ARA-C), 6-thioguanine (TG), and methotrexate (MTX).

Maintenance chemotherapy was based on 6-mercaptopurine.

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death or relapse, or to date of last control, by life-table analysis. All p values were used throughout. Survival and CR length were on the comparison of the number of deaths or relapses observed (0) survival) was analyzed by the chi-square test and by the log rank Statistical Procedures was dependent on CR rate and on first CR length. Therefore, examined until May 1981. On that date, 59 patients were alive and to follow-up after 9-15 mo. All the other patients were regularly the cause, were included in the calculation. Three patients were lost (6-MP) (50-80 mg/sq m/day and MTX (25-35 mg/sq m/wk), but included also pulses of VCR and P (165 cases), DAUNO (76 cases), ARA-C (38 cases), TG (25 cases), CYCLO (17 cases), ASP (5 cases), and a nitrosourea (3 cases). Maintenance chemotherapy was discontinued after 24-60 mo of continuous CR.

CNS prophylaxis by i.t. chemotherapy (4-6 doses of MTX and/or ARA-C) or by combined i.t. chemotherapy and cranial irradiation (2100-2400 rad) was given to 91% of patients who achieved CR. Patients who received only i.t. chemotherapy were continued on intermittent it. chemotherapy and cranial irradiation.

Statistical Procedures

The relationship of each feature (or combination of features) to prognosis (outcome of remission induction, length of first CR, and survival) was analyzed by the chi-square test and by the log rank method (testing for heterogeneity between pairs and for trend among 3 or more groups). The test for heterogeneity and for trend was based on the comparison of the number of deaths or relapses observed (O) in each group of patients, with the extent of exposure (E) to risk of death or relapse in that group. E was calculated by dividing the number of events (deaths or relapses) on each day by the proportion of patients in each group remaining at risk on that day, and adding all E values up to get the total extent of exposure to risk.28 Two-tailed p values were used throughout. Survival and CR length were calculated from date of diagnosis and CR, respectively, to date of death or relapse, or to date of last control, by life-table analysis.29 All relapses, hematologic and nonhematologic, and all deaths, whatever the cause, were included in the calculation. Three patients were lost to follow-up after 9-15 mo. All the other patients were regularly examined until May 1981. On that date, 59 patients were alive and relapse-free with a median follow-up time of 47 mo (range 17-125 mo).

In this series, as in many studies of ALL, the length of survival was dependent on CR rate and on first CR length. Therefore, analytical data on survival are omitted, as they are a mere repetition of data on CR rate and length.

RESULTS

CR was obtained in 232 of 293 patients or 79.2% (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 × 10⁹/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 × 10⁹/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 × 10⁹/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 to a high WBC count (8 of 14 patients, or 57%, had a WBC count higher than 35 × 10⁹/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.
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></td>
<td></td>
<td></td>
<td>O</td>
<td>E</td>
</tr>
<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>p &lt; 0.70</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>L1 + L2 vs L3</td>
<td></td>
<td>p &lt; 0.60</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>Membrane Marker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E SmIg</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>SmIg'</td>
<td>9 (7%)</td>
<td>6 (67%)</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>E SmIg' vs E'</td>
<td></td>
<td>p &lt; 0.60</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>E SmIg + E' vs SmIg'</td>
<td></td>
<td>p &lt; 0.30</td>
<td></td>
<td>E</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:

- 682 patients had received CNS prophylaxis and all but one were in first continuous CR after more than 5 yr.
- 385 patients had been given maintenance chemotherapy with at least 4 drugs. Interestingly, 2 of 5 patients with FAB L3 cytotype, and 1 of 2 patients with E blast cells were in remission.
- There was no difference among patients who had been on therapy for 1-9 mo (median 6 mo), and those who had been off therapy for 10-90 mo (median 44 mo).
- Age was unrelevent to long-term prognosis: 26% of male relapses, but their influence on first CR was not clearly related to increasing age. A worse prognosis, as compared to children less than 10 y old, was observed in adolescents and adults who had been on therapy for 24-60 mo (median 36 mo), and they were more likely to have testicular relapse, as in children.

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>Age &lt; 30 yr</td>
<td>62%</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 30-40 yr</td>
<td>26%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 40 yr</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>62%</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>38%</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &gt; 35 x 10^9/liter</td>
<td>31%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &gt; 10 x 10^9/liter</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 20 x 10^9/liter</td>
<td>32%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 10 x 10^9/liter</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 0.5 x 10^9/liter</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 0.3 x 10^9/liter</td>
<td>1%</td>
<td></td>
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</tbody>
</table>

The three features that were significantly associated with a relapse-free survival longer than 5 yr, demonstrated that adolescents (11-13 yr) had a WBC < 33 x 10^9/liter, and p < 0.005 for WBC > 35 x 10^9/liter. There was no difference among patients who were between 10 and 20 x 10^9/liter and those who were between 20 and 25 x 10^9/liter. The features of age on prognosis depended much more on CR rate than first CR length. In fact, apart from the small group of patients aged above 60, the probability of remaining in first CR length. This relationship of young age to CR rate, but not to first CR length, was also found by Omura et al. and by Brun et al. This study provided unequivocal evidence in adolescents and adults that WBC count was always associated to hematologic relapse.
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 ($\geq 30$ 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 ($> 35 \times 10^9$/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 $< 35 \times 10^9$/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.
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