Immunophenotype of Adult Acute Lymphoblastic Leukemia, Clinical Parameters, and Outcome: An Analysis of a Prospective Trial Including 562 Tested Patients (LALA87)

By Claude Boucheix, Bernard David, Catherine Sebban, Evelyne Racadot, Marie-Christine Bené, Alain Bernard, Lydia Campos, Hélène Jouault, François Sigaux, Eric Lepage, Patrick Hervé, and Denis Fiére for the French Group on Therapy for Adult Acute Lymphoblastic Leukemia

The aim of the multicentric trial LALA87 was to test the efficacy of different postremission therapies in adults (15 to 60 year olds) with acute lymphoblastic leukemia (ALL). An immunologic subclassification based on surface marker expression was proposed. Among the 562 tested patients, 511 were assigned either to the B lineage (361 cases, 63%) or to the T lineage (150 cases, 26%). T-ALL were significantly associated with male sex, age less than 35 years, mediastinal mass, central nervous system involvement, high white blood cell count, and low anemia. In a univariate and multivariate analysis, T-cell leukemia had a more favorable outcome than B-cell leukemia with respective median disease-free survivals (DFSs) of 28 and 14 months (P < .005). However, the type of postremission therapy modifies the value of the immunophenotype prognostic factor. In the chemotherapy arm, T-ALL patients (26 patients) had a more favorable outcome than B-ALL patients (57 patients) (P < .003). In the autologous bone marrow transplantation (ABMT) arm, the apparent better outcome of T-ALL patients (36 T/50 B) did not reach statistical significance (P = .2) and there was no difference in the allogeneic bone marrow transplantation (alloBMT) arm (37 T/71 B: P = .9). In the B-cell-lineage leukemias, subclassification by stages and myeloid antigen coexpression (10%) were not associated with different prognosis. CD10+ T-ALL (31 patients) were associated with a better DFS compared with the CD10+ T-ALL (73 patients) with respective median DFS, not reached and 18.5 months (P = .04). © 1994 by The American Society of Hematology.

THE RELATIONSHIP between lymphoid ontogeny and human acute lymphoblastic leukemia (ALL) has been more precisely unravelled by the description of the differentiation pathways of the T- and B-lymphoid lineages18. The sequence of events leading to the development of mature lymphoid cells is associated with cell surface modifications that can be easily analyzed by the use of monoclonal antibodies (MoAbs). The importance of the immunophenotypic analysis of ALL has been documented by numerous studies in adults and children. However, the great number of phenotypic patterns has introduced a further level of complexity in the classification of ALL. If certain leukocyte differentiation antigens used for these analyses show some level of lineage specificity (for instance the CD3 T-cell lineage), other surface molecules display a wider tissue distribution. For instance, the CD10/CALLA antigen initially described in non-T leukemia2 and now identified as neutral endopeptidase, has a large tissue distribution, but its transient expression during B-cell differentiation helps to define a particular stage; it is also expressed on a fraction of T-ALL (for review, see Lebien and McCormack). On the other hand, the myeloid markers CD13 and CD33 have not been found on normal lymphoid cells and their expression in some ALL has been referred to as myeloid antigen coexpression. The clinical significance of the presence of myeloid markers has been widely debated, but because of the small size of some of the patient groups, the mixture of adult and pediatric cases and the differences in the treatment protocols, no final conclusions can be drawn from studies completed thus far.

Beside immunophenotyping aspects, the heterogeneity of the disease is observed at both clinical (age of onset, sex, symptoms, and prognosis) and biologic levels (cytology and cytogenetic aspects). Despite some recent progress, the prognosis of adult ALL remains poor. If complete remission (CR) can be achieved in 70% to 80% of patients, relapses occur frequently and long-term disease-free survival (DFS) does not exceed 25% to 30%.20-25 Three kinds of postremission therapy can be proposed: chemotherapy (CT), allogeneic bone marrow transplantation (alloBMT)26-27 and autologous bone marrow transplantation (ABMT).28-30 Only multicentric studies with random assignment and careful analysis might help to define adapted therapies in relation to the diversity of the disease.

Patients included in a large French multicentric trial LALA831 were submitted to an initial evaluation including immunological phenotyping. This report describes immunological phenotypic data and analyzes their relationships with clinical characteristics and outcomes. The main objective was to assess the relevance of a reliable immunologic classification with three objectives: (1) to identify a clinical and biologic profile according to phenotypic subgroups; (2) to assess the effect of phenotype on outcome; and (3) to evaluate the optimal postremission therapy in each group.

MATERIALS AND METHODS

Patients

From November 1, 1986 to July 31, 1991, 634 patients treated in 43 hematologic centers entered the LALA87 trial. Eligibility criteria included patients treated in 43 hematologic centers entered the LALA87 trial. Eligibility criteria

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were morphologically\textsuperscript{32} and cytochemically confirmed diagnosis of ALL (L3 FAB subtype excluded), absence of prior malignancy, severe illness or psychiatric disease, and age from 15 to 60 years. After exclusions, 572 patients were analyzed. Median age of the population was 33 years.

The design of the protocol and the main clinical results have been reported elsewhere.\textsuperscript{33} The general design with the flow chart of the patients is summarized in Fig 1. Briefly, eligible patients were submitted to an induction CT regimen including cyclophosphamide, vincristine, prednisone, and a random allocation between two anthracyclines (daunorubicin or zorubicin). If CR was not obtained at day 28, a salvage therapy with amsacrine and cytosine arabinoside was administered. A central nervous system (CNS) prophylaxis was administered.  

A central nervous system (CNS) prophylaxis was associated. Patients from 15 to 40 achieving CR, with an available HLA-compatible sibling donor were scheduled for alloBMT. Patients over 50 years received consolidation and maintenance CT. Patients from 40 to 50 years and patients up to 40 without HLA sibling donor were scheduled for an induction CT regimen including cyclophosphamide, vincristine, prednisone, and a random allocation between two anthracyclines (daunorubicin or zorubicin). If CR was not obtained at day 28, a salvage therapy with amsacrine and cytosine arabinoside was administered. A central nervous system (CNS) prophylaxis was associated. Patients from 15 to 40 achieving CR, with an available HLA-compatible sibling donor were scheduled for alloBMT. Patients over 50 years received consolidation and maintenance CT. Patients from 40 to 50 years and patients up to 40 without HLA sibling donor were randomized after a first course of consolidation between consolidation and maintenance CT or consolidation and ABMT. They received in both arms these courses of consolidation including the anthracyclines used for induction, cytosine arabinoside and L-Asparaginase (modified 3A protocol). In the CT arm, the maintenance CT consisted of eight cycles of the L10 modified protocol.\textsuperscript{33} In the ABMT arm, the protocol assumed MoAb depletion of the BM by the MoAbs D66/CD2, A50/CD5, and I21/CD7 (provided by A. Bernard) for T-ALL and the MoAbs ALBZKDlO (Immunotec, Marseille) and SB4/CD19 (Sanofi, Montpellier, France) for B-ALL. Asta-Z (Asta Werke, Frankfurt, Germany) depletion was proposed for patients with less than two of these markers on their leukemic cells.

Stopping date was set for September 1992. Median follow-up was 33 months. Four hundred and thirty six patients (78\%) achieved CR after induction or induction and salvage therapy. One hundred and sixteen patients were scheduled to receive alloBMT with an estimated 3-year DFS rate of 43% \pm 5\%. The ABMT arm (95 patients) and CT arm (96 patients) produced comparable 3-year DFS rates (39\% \pm 32\%). Patients over 50 years had a 3-year DFS rate of 24\%.

**Immunophenotype Analysis**

To classify the disease according to the differentiation pathways and to choose appropriate antibodies in case of BM depleted autograft, heparinized BM or blood samples were used for immunophenotyping using a panel of MoAbs. Immunophenotyping was usually performed on BM cells by indirect immunofluorescence and flow cytometry, to analyze a pure (or nearly pure) blast cell population. The immunologic classification used in this trial was based on the expression of the CD1, CD2, CD3, CD5, CD7, CD4, CD8, HLA-DR, CD10, CD19, CD20 markers and the absence of surface IgS. However, it had been suggested that the panel of antibodies tested be extended. Therefore numerous patients were tested also for CD9, CD13, CD24, CD33, and HLA class II antigens.

Because of the large number of centers involved in the study, the origin of the MoAbs varied from one center to another, but the different antibodies belonged to the same cluster according to the CD nomenclature.\textsuperscript{34,35} Results were reviewed, interpreted, and registered in an independent database (with the same entry number as the main database) by an immunologic committee that issued regular information to the centers involved in the trial. After reinterpretation and correction for the blast cell percentage and negative controls, the arbitrary threshold of 20\% labeled blast cells was considered the limit for positivity of a given marker (20\% blast cells expressing the antigen). If necessary, the immunologic committee requested new testing of the cells with additional MoAbs on cryopreserved cells. The fusion between the complete immunologic database with the main database was performed in January 1993.

We proposed an immunologic classification B1, B2, B3A, B3B, T1A, T1B, T2, T3, as defined in Fig 2. To reduce the number of subgroups, the lineage assignment was determined by the presence of the pan-lineage markers, CD19 for the B-cell lineage, CD2/CD5/CD7 for the T-cell lineage. The level of differentiation was evaluated by the presence of the CD10 and CD20 antigens for the B-cell lineage and the CD4 and CD3 antigens for the T-cell lineage. For the latter, in the absence of CD3 or CD1 expression or in the absence of testing, the presence of the CD4 and/or CD8 markers was considered reflecting a higher level of differentiation and assigned these patients to a T2T3 subgroup. Classification in intermediate stages or only within the T-cell lineage was decided in the absence of testing of differentiation stage markers. Finally, in cases of coexpression, the most differentiated marker was considered for the classification; eg, coexpression of CD1 and CD3 assigned the leukemia to the T3 stage.

**Statistical Methods**

The endpoints were CR rate, overall survival, and DFS. Survival duration was calculated from the date of randomization until death.
or date last known alive. DFS was calculated from date of CR until relapse or last known survival date in CR. Deaths in CR were counted as adverse events. Survival curves were estimated by the method of Kaplan and Meier. Univariate analyses were performed using the chi-square test and the generalized Wilcoxon test of Gehan. Test statistics for comparison of endpoints were regarded as significant if the P value was < .05. All survival analyses were made on an intention to treat basis. Multivariate analyses of prognostic factors were performed according to Cox's proportional hazard model for covariate analysis of censored survival data.

RESULTS

General Characteristics of Immunophenotypic Data

As shown in Table 1, 572 patients (15 to 60 years old) were evaluable for clinical analysis. Immunophenotyping was not performed in 10 patients. According to our criteria, 511 patients over 562 (90.9%) could be assigned to the B lineage (361 cases, 63%) or to the T lineage (150 cases, 26%). Fifteen patients (2.7%) were negative for all markers of the B or T cell lineages, and thus were considered as undifferentiated. Because of insufficient data, 36 patients (6.2%) remained unclassified (UC); in 9 of these patients, the inability to perform a significant immunophenotype could be related to BM fibrosis. The distribution related to the stage of differentiation and lineage involvement is shown on Table 1. Terminologies such as B1B2 or T1T2 indicate that one or several markers were not tested precluding a more accurate classification.

Comparative Clinical Analysis of the Major Immunophenotype Groups

Main pretherapeutic characteristics. Clinical and biologic characteristics, related to each type and subtype, are reported in Table 2 for all patients between 15 and 60 years old. T-ALL and B-ALL significantly differed in their presentation. Patients with T-ALL were statistically significantly younger (77% of them are younger than 35 years; v 50% for B-ALL: P < .001). Patients with T-ALL were more often male (75% v 55% in B-ALL, P < .001). Mediastinal mass was present in 49% of T-ALL versus 2% in B-ALL (P < .001) and white blood cell (WBC) count was greater than 30 × 10^9/L in 55% of T-ALL versus 30.5% in B-ALL (P < .001). Anemia was less frequent in T-ALL (65% v 85% in B-ALL, P < .001). CNS involvement was observed in 10.5% of T-ALL whereas it was present in only 5% of B-ALL (P < .04).

Relationships between phenotype and outcome. As shown in Table 2 for all patients from 15 to 60 years, global CR rates were 81% for T-ALL and 74% for B-ALL. This difference was not statistically significant (P = .08). For T-ALL, 106 patients over 150 (71%) achieved CR at day 28 after the start of the induction course and of the 38 patients who received the scheduled salvage therapy with amsacrine and cytosine arabinoside, 16/38 (42%) patients achieved CR. For B-ALL, 248 patients over the 361 achieved CR at day 28 (69%) and among the 68 patients who received the salvage therapy, 19 (28%) of them achieved CR.

Patients with T-ALL had a significantly better DFS and better overall survival when compared with patients with B-ALL. The respective median DFS for T- and B-ALL were...
Table 2. Main Clinical and Biologic Characteristics of Immunophenotypic Subgroups in the LALA87 Trial Including All Analyzed Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>B</th>
<th>T</th>
<th>P (B:T)</th>
<th>U</th>
<th>B1</th>
<th>B2</th>
<th>B3 (A + B)</th>
<th>T1A</th>
<th>T1B</th>
<th>T2</th>
<th>T3</th>
</tr>
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<tr>
<td>No.</td>
<td>361</td>
<td>150</td>
<td>16</td>
<td>45</td>
<td>142</td>
<td>131</td>
<td>11</td>
<td>27</td>
<td>40</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Age (median)</td>
<td>34.5</td>
<td>25</td>
<td>37</td>
<td>36</td>
<td>33.5</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>23</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>≤35 yrs (no.)</td>
<td>183 (60%)</td>
<td>115 (76.7%)</td>
<td>.&lt;.001</td>
<td>21 (46.7%)</td>
<td>75 (52.8%)</td>
<td>66 (50.4%)</td>
<td>9 (81.8%)</td>
<td>22 (81.5%)</td>
<td>30 (75%)</td>
<td>32 (74.4%)</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>198/163</td>
<td>114/36</td>
<td>.&lt;.001</td>
<td>11/5</td>
<td>18/27</td>
<td>77/65</td>
<td>73/58</td>
<td>9/2</td>
<td>20/7</td>
<td>29/11</td>
<td>38/5</td>
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<tr>
<td>WBC 10^9/L (median)</td>
<td>12.1</td>
<td>44</td>
<td>.&lt;.001</td>
<td>27</td>
<td>16.8</td>
<td>12.5</td>
<td>13</td>
<td>23.5</td>
<td>67.5</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>≥30 × 10^9/L (no.)</td>
<td>110 (30.5%)</td>
<td>85 (55.4%)</td>
<td>27</td>
<td>19 (42.2%)</td>
<td>42 (29.6%)</td>
<td>41 (31.3%)</td>
<td>6 (54.5%)</td>
<td>17 (53%)</td>
<td>23 (57.5%)</td>
<td>22 (51.2%)</td>
<td></td>
</tr>
<tr>
<td>Platelets 10^11/L (median)</td>
<td>57</td>
<td>70</td>
<td>129</td>
<td>75</td>
<td>56</td>
<td>53</td>
<td>87.5</td>
<td>72</td>
<td>70</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>≤100 × 10^11/L (no.)</td>
<td>250 (70%)</td>
<td>101 (67.8%)</td>
<td>NS</td>
<td>27 (60%)</td>
<td>99 (69.7%)</td>
<td>95 (72.5%)</td>
<td>7 (63.6%)</td>
<td>19 (70.4%)</td>
<td>26 (62.6%)</td>
<td>31 (72%)</td>
<td></td>
</tr>
<tr>
<td>Hb g/L (median)</td>
<td>90</td>
<td>109</td>
<td>84</td>
<td>92</td>
<td>89</td>
<td>90</td>
<td>85.1</td>
<td>106</td>
<td>120</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>≥120 g/L (no.)</td>
<td>302 (85.3%)</td>
<td>97 (64.7%)</td>
<td>.&lt;.001</td>
<td>38 (84.4%)</td>
<td>119 (83.8%)</td>
<td>114 (87%)</td>
<td>11 (100%)</td>
<td>20 (74%)</td>
<td>24 (60%)</td>
<td>24 (55.8%)</td>
<td></td>
</tr>
<tr>
<td>Mediastinal mass (%)</td>
<td>2.2</td>
<td>48.6</td>
<td>.&lt;.001</td>
<td>0</td>
<td>2.2</td>
<td>0.7</td>
<td>3.9</td>
<td>27</td>
<td>46</td>
<td>52.5</td>
<td>57</td>
</tr>
<tr>
<td>CNS (%)</td>
<td>5.3</td>
<td>10.5</td>
<td>.&lt;.04</td>
<td>13</td>
<td>4.6</td>
<td>2.9</td>
<td>10.1</td>
<td>9</td>
<td>20</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>CR (%)</td>
<td>74</td>
<td>81</td>
<td>.&lt;.07 (NS)</td>
<td>73</td>
<td>71</td>
<td>70</td>
<td>80</td>
<td>54</td>
<td>74</td>
<td>87.5</td>
<td>91</td>
</tr>
<tr>
<td>Median survival (mos)</td>
<td>16</td>
<td>25</td>
<td>.001</td>
<td>19</td>
<td>12.5</td>
<td>15</td>
<td>17</td>
<td>15</td>
<td>17</td>
<td>NR</td>
<td>22</td>
</tr>
<tr>
<td>% 3-yr survival (± SE)</td>
<td>32.4 (2.7)</td>
<td>48.9 (4.2)</td>
<td>23.3 (11.5)</td>
<td>33.3 (7.3)</td>
<td>29.3 (4.4)</td>
<td>35.5 (4.5)</td>
<td>36.3 (14.5)</td>
<td>42.9 (9.7)</td>
<td>61.7 (7.8)</td>
<td>49.9 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Median DFS (mos)</td>
<td>14</td>
<td>28</td>
<td>.005</td>
<td>13</td>
<td>10.5</td>
<td>13.5</td>
<td>15</td>
<td>27.7</td>
<td>15.5</td>
<td>NR</td>
<td>18.5</td>
</tr>
<tr>
<td>% 3-yr DFS (± SE)</td>
<td>30.9 (3)</td>
<td>48.2 (4.7)</td>
<td>27.3 (13.4)</td>
<td>28.8 (8.3)</td>
<td>26.7 (5)</td>
<td>35.1 (4.9)</td>
<td>50 (20)</td>
<td>39.7 (12)</td>
<td>61.2 (8.4)</td>
<td>40.6 (8)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: UD, undifferentiated; NS, not significant; NR, not reached.
28 months and 14 months (P = .005). Respective overall survival for T- and B-ALL were 25 months and 16 months (P = .001). In a multivariate analysis, T phenotype was found as an independent favorable prognostic factor (P = .004) as well as initial WBC count less than 30 x 10^9/L (P < .001) for overall survival. For DFS, T phenotype was also found as an independent prognostic factor with age less than 35, initial WBC count less than 30 x 10^9/L and platelets greater than 100 x 10^9/L (P < .001).

**Impact of the phenotype group on the outcome of the different postremission therapies.** When stratifying according to the different post-remission therapy regimens (CT arm, allo-BMT arm and ABMT arm) a statistically significant difference between the outcome of T- and B-ALL was only observed in the CT arm (Fig 3). The relapse rate for T-ALL was identical in each arm, but varied considerably for B-ALL.

Among the 96 patients randomized in the CT arm, 26 of them (27%) were T-ALL, whereas 57 (59%) were B-ALL. There was a better DFS for patients with T-ALL, with a median DFS not reached compared with 16 months for patients with B-ALL, and a 3-year DFS probability rate of 59% for T-ALL versus 20% for B-ALL (< .003).

Among the 95 patients randomized in the ABMT arm, 35 of them (37%) were T-ALL, whereas 50 (53%) were B-ALL. The observed difference favoring T-ALL was not statistically significant (P = .2). Median DFS was not reached for T-ALL, but was 12 months for B-ALL. The respective 3-year DFS probability rates were 51% and 35%.

Among the 116 patients scheduled for alloBMT, 25 of them (32%) had T-ALL, whereas 71 (61%) had B-ALL. The outcome for T- and B-ALL was similar with respective median DFS of 22 and 23 months and respective 3-year survival probability rates of 44% and 45% (P = .9).

To illustrate the influence of postremission therapy on the outcome according to the immunologic phenotype, Fig 3 displays the DFS curves for all patients ≤ 40 years according to the three therapies.

**Immunologic Subclassification and Clinical Outcome**

**B-lymphoid lineage ALL.** It was possible to make an accurate assignment, using the classification proposed above, for 318/361 of the B-lineage ALL (88%) with a large majority of B2 (40%) and B3A subtypes (32%). For these 318 patients accurately assigned to a given subgroup of the B-lymphoid lineage (B1,B2,B3), no difference between these different immunologic subgroups was observed in terms of CR rate, DFS, and overall survival (Fig 4).

The presence or absence of CD10 antigen did not change survival parameters. Myeloid antigen coexpression CD13 and/or CD33 was examined in 282 of these patients; leukemic cells of 25 patients (8.9%) were positive for at least one of the two markers. CD13 was observed in 16/258 patients, CD33 was observed in 15/249 patients. Among the 20 positive patients tested for both markers, 6 expressed simultaneously CD13 and CD33. No significant relationship with the differentiation stage was detected and no effect on survival could be observed by statistical analysis. A number (91.4%,...
The level of differentiation was not related to the other main parameters such as age or WBC count.

T-lymphoid lineage ALL. For the T-lymphoid lineage, an accurate differentiation stage assignment was possible for 81% of the 150 cases. T-cell ALL were almost equally distributed among the three levels of differentiation with T1 (30, 6%), T2 (26, 6%), and T3 (28, 7%). The evolution according to the level of differentiation (T1A, T1B, T2, T3) did not show significant differences between the subgroups. Comparisons on the basis of individual markers showed no significant differences in terms of DFS according to the presence of either CD1 or CD3. However, the 3-year survival was significantly better for patients whose cells expressed the CD1 antigen (63% for CD1+ patients, 42% for CD1− patients, $P = .03$).

Among the 130 patients with T-ALL tested for CD10, 38 of them (29%) expressed CD10, whereas 92 (71%) did not express CD10. Best overall survival was for CD10+ T-ALL patients, but the trend was not significant ($P = .06$). However, there was a favorable outcome for DFS of the T-ALL patients with CD10 antigen on leukemic cells (Fig 5). The frequency of CD10 expression increased with the level of differentiation; as to the age, 26 of 99 (26%) below 35 years and 12 of 31 (39%) above 35 years were CD10+. In contrast, HLA class II (12/131 tested, 9%) and CD9 antigen expression (20/101 tested, 19.8%) were not correlated with the prognosis.

Myeloid antigen coexpression (CD13 and/or CD33) was examined in 117 patients; leukemic cells of 12 patients (10.2%) were positive for at least one of the two markers, more frequently CD33 than CD13. Indeed, CD13 was observed in 4 of 107 patients, whereas CD33 was observed in 10 of 95 patients. Among the 11 positive patients tested for the two markers, 2 of them expressed both. A significant relation with the differentiation stage was detected because 4 of 11 T1A were positive with 9 of 44 for the whole T1 stage, whereas only 2 of 30 and 2 of 32 were positive for the T2 and T3 stages, respectively. Because the criteria of inclusion were morphologic and cytochemical, we can't exclude that some of the T1A patients had M0 AML.

Undifferentiated ALL. The number of patients with undifferentiated ALL (15 cases) was too small for evaluating
a prognosis impact. On the whole, the outcome of these patients was similar to that of B-lineage-related ALL. Twelve patients were tested for myeloid markers and only one of them was positive (CD13); 10 of the 11 patients tested for HLA class II were positive.

Prognostic Factors According to Immunophenotype Groups: Univariate and Multivariate Analysis

Initial WBC count and age are the most commonly described prognostic factors in adult ALL. They were validated in the LALA87 trial. When looking at the influence of the phenotype on these parameters in a univariate analysis, it appears that the WBC count was the most important prognostic factor in the B-lineage ALL, whereas age was the most important criterion for T-ALL. The main outcomes according to age and WBC count for B- and T-ALL are detailed in Table 3.

A multivariate analysis was performed in T-ALL with age, WBC count, platelets, and presence or absence of CD10 antigen. Only WBC count ($P = 0.05$) was found for overall survival, whereas for DFS, age less than 35 ($P = 0.04$), WBC count less than $30 \times 10^9/L (P < 0.001)$, and presence of CD16 ($P = 0.001$) were three independent favorable prognostic factors. Similarly, in B-ALL, WBC count was the only prognostic factor found for overall survival ($P = 0.02$) whereas WBC count less than $30 \times 10^9/L (P < 0.001)$ and platelets greater than $100 \times 10^9/L (P < 0.001)$ were found as the two independent favorable prognostic factors for DFS.

DISCUSSION

A considerable number of markers is presently available for the immunophenotyping of ALL. In the LALA87 trial, we tested a set of markers commonly used in 1987 to evaluate the prognostic impact of an immunologic classification on the outcome of patients included in this protocol and to search for an adapted therapeutic strategy. All patients were submitted to a similar induction protocol and postremission was randomly allocated according to age and availability of a HLA sibling donor. Furthermore, most of the included patients benefited from an accurate immunologic analysis allowing clinicobiologic correlations. The previously re-

![Fig 5. DFS curves of CD10 + versus CD10 - T-ALL. (n.r., not reached)](image)

<table>
<thead>
<tr>
<th>Table 3. Relevance of the Usual Prognosis Criteria of Adult ALL According to the B or T Immunophenotype for All Patients Analyzed</th>
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<tbody>
<tr>
<td><strong>Expression</strong></td>
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<tr>
<td>----------------</td>
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<td>WBC $&lt; 30 \times 10^9/L$</td>
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<td>T-ALL</td>
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Abbreviation: NR, not reached.
ported difference in the clinical presentation and the prognosis between T- and B-lineage leukemias appears to be very significant in this trial. We confirmed the generally better outcome of T-ALL and our results are consistent with the fact that T-ALL and B-ALL are two distinct clinical entities. The favorable impact of T phenotype was found in this trial in a large multivariate analysis on both overall survival and DFS. A further level of stratification introduced by the investigation of cytogenetic and molecular rearrangements would be important, at least for B-ALL, because patients with bcr-ab1 rearrangement have a poor prognosis. In the LALAS7 trial, karyotype was performed in 274 patients and Ph chromosome was found in 58; because CR was obtained in only 57% of these patients and only one of them is still alive, these patients contribute to the poor prognosis of B-ALL in this trial.

Interestingly, the outcomes with the available postremission therapy regimens strongly differ especially in the alloBMT arm where the difference between the B- and T-cell leukemias disappeared. No statistical difference was observed in the ABMT arm. However, the lack of statistical significance could be explained by the small sample size of each patient group. Indeed, there is no obvious reason for this difference of outcome according to the type of postremission therapy. Nevertheless, it has to be noticed that patients in the alloBMT arm did not receive cytosine arabinoside, which is considered to be a very effective drug in T-ALL.

The immunophenotypic subclassification of B cell leukemias did not show significant differences according to the level of differentiation. The usual comparison of CD10 versus CD10 non T-ALL (usually referred as null-ALL) is not very informative. It has to be noticed that the CD10 non T-ALL, frequently grouped in the literature are a mixture of undifferentiated, B1, and B3B ALL in the classification used in this trial. In our opinion, there is not longer any biologic relevance to classifying ALL in this way. cytoplasmic μ chains, not included in this study for technical reasons, are an additional potentially useful marker; they are usually associated with late differentiation stages of B-ALL, but they do not fit strictly within a given stage of the classification proposed in this study.

The incidence of myeloid antigen coexpression as judged by the presence of the CD13 or CD33 antigens was limited to less than 10% of the patients and no clinical correlation could be observed. The frequency and clinical importance of myeloid markers has often been reported in the literature; however, no satisfactory interpretation can be drawn from these studies because results are contradictory. In the large series of 633 children from Ludwig et al, the 43 B-ALL patients with myeloid markers had a high remission rate and the LFS was identical to the corresponding myeloid marker-negative patients; also, Bradstock et al did not observe adverse effects of myeloid markers in a mixed population of adult and children with B-ALL.

On the other hand, Sobol et al observed myeloid antigen coexpression in 17 of 55 adult B-ALL and they reported a lower rate of CR and a shorter survival. Large numbers of uniformly treated patients are needed to assess the prognosis of these markers within a given protocol.

Subclassification of T-ALL showed no significant differences. However, the T1A group (11 patients with isolated CD7 positivity), seemed to have a slightly worse prognosis in terms of survival. An interesting point in the group of T-ALL is the impact of the CD10 expression; the CD10 ALL (30% of T-ALL) had a better prognosis than the CD10 non, even when using a multivariate analysis. A similar conclusion was drawn from a large study in childhood ALL. In this trial, CD10 expression seems to be an independent prognostic factor that needs to be confirmed by other studies. On the other hand, no effect on prognosis of the HLA class II (8% of the T-ALL) marker was observed. Regarding the 13 cases of myeloid antigen coexpression (9%) in T-ALL, most of them were found in early differentiation stages. The biologic significance of these leukemias and related normal cells has been addressed in several papers; in some cases, it has been shown that the leukemic cells gave rise to both T-cell and myeloid colonies in vitro.

In conclusion, this study, within the limits of the treatment regimens, supports some previous observations on the link between immunologic phenotype and prognosis for the major T- and B-cell–lineage–related adult ALL. The design of the trial outlines some particular findings such as the loss of prognostic significance of the immunophenotype for patients receiving alloBMT in first remission and the different values of classical prognostic parameters between T- and B-cell leukemia. These statements need to be confirmed by other studies to be incorporated in the design of future therapeutic trials.

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