Adult Acute Lymphoblastic Leukemia Phenotypes Defined by Monoclonal Antibodies


PRETREATMENT peripheral blood and/or bone marrow blasts from 90 adults with acute lymphoblastic leukemia (ALL) were analyzed as part of a prospective treatment protocol study. Specimens were tested by immunofluorescence cytofluorometry for reactivity with the following monoclonal antibodies (MoAbs): BA-1 (B cell antigen); T101, OKT11 (pan-T cell antigens [T]); 3A1 (T cell antigen); MCS-2 (myeloid antigen); J5 common ALL antigen (CALLA); BA4 (Ia antigen [Ia]); BA-2 (lymphohematopoietic antigen). Four major phenotypic groups were identified: B lineage ALL (BA-1 T) (64%), T lineage ALL (T9 BA-1 MCS-2) (13%), unclassified ALL (BA-1 MCS-2 CALLA T) (9%) and myeloid antigen ALL (MCS-2 CALLA T) (7%). An additional group of patients, miscellaneous ALL (7%), was comprised of cases with unusual marker profiles. In B lineage ALL, all cases tested were Ia' MCS-2', and the vast majority were CALLA' (84%). In T lineage ALL, 42% expressed CALLA or Ia positivity. In unclassified ALL, the predominant phenotype was Ia' BA-2'. In myeloid antigen ALL, two of four tested were 3A1'. And all cases evaluated were BA-1. Patients with myeloid antigen ALL were older (median age, 66 years) than patients in the other groups. The T lineage ALL group had higher leukocyte counts (median WBCs, 183,000/μL) and an increased incidence of anterior mediastinal mass at presentation. All patients received identical induction therapy. In CALLA' B lineage ALL, 30 of 46 (65%) achieved a complete remission. While the number of patients evaluated was small, 9 of 8 CALLA' B lineage ALL and only two of six myeloid antigen ALL cases responded with a complete remission. The data suggest that these MoAbs are useful in the characterization of adult ALL.

CONVENTIONAL hematopoietic cell marker analyses have proven useful in the clinical evaluation of acute lymphoblastic leukemia (ALL) and in furthering our understanding of normal lymphoid differentiation. It is generally accepted that children with lymphoblasts expressing surface immunoglobulin (slg) or E rosette formation (E), have distinctive clinical features at presentation and a poorer prognosis than those whose lymphoblasts do not express these conventional B or T cell markers. However, conventional marker studies employing polyclonal antisera, rosetting, and cytochemical techniques are prone to inaccuracies introduced by the variable specificity of the antibody reagents and the difficulties of standardizing the rosetting and cytochemical assays. The development of the technique for the production of monoclonal antibodies (MoAbs) by somatic cell hybridization offers the advantages of large-scale production and universal availability of standardized monospecific reagents.

Several investigators have utilized MoAbs directed against previously defined and novel hematopoietic antigens to confirm and extend the characterization of ALL. Yu et al.11 in a study of childhood ALL utilizing anti-Ia and pan-T cell (T101) MoAbs, found that the Ia' T101 phenotype was associated with good prognostic factors and longer median disease-free survival than Ia T101' marker profiles. Included in the Ia T101' group were several E rosette negative cases with clinical features of T cell disease. Reinherz and co-workers,12 employing a panel of MoAbs to T cell antigens, identified several different T-ALL phenotypes; their findings suggest that T-ALL may represent a more heterogenous subgroup of ALL than previously recognized. More recently, Korsmeyer et al.13 correlated MoAb-defined phenotypes with immunoglobulin (Ig) gene rearrangements to evaluate the lineage of ALL-derived lymphoblasts. T cell antigen-negative cases expressed either Ia, B cell antigen (BA-1) or common ALL antigen (CALLA) positivity, and exhibited Ig gene rearrangements implying B cell origin. All T cell antigen-positive cases had a germ-line heavy or light chain gene configurations.

Because the majority of patients evaluated in these previous studies were children, the present investigation was performed to examine the marker characteristics of a large series of prospectively studied adult ALL patients. Leukemic blasts were tested for reactivity with a panel of MoAbs directed against hematopoietic antigens and with conventional lymphocyte marker analyses. Correlations of adult ALL MoAb-defined phenotypes with clinical features and with previously reported ALL marker profile classifications are discussed. A hypothesis of early lymphoid differentiation based upon the phenotypes defined by MoAb analysis is presented.
ADULT ALL PHENOTYPES

Table 1. MoAbs Utilized for Adult ALL Phenotype Determination

<table>
<thead>
<tr>
<th>MoAb</th>
<th>Isotype</th>
<th>Reactivity</th>
<th>Antigen Molecular Weight</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>J5</td>
<td>lgG2</td>
<td>CALLA</td>
<td>100,000</td>
<td>19</td>
</tr>
<tr>
<td>BA4</td>
<td>lgG1</td>
<td>HLA-DR (Ia)</td>
<td>29,000</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34,000</td>
<td></td>
</tr>
<tr>
<td>BA-1</td>
<td>lgM</td>
<td>B cells and mature granulocytes</td>
<td>45,000*</td>
<td>20</td>
</tr>
<tr>
<td>BA-2</td>
<td>lgG1</td>
<td>Lymphohematopoietic antigen</td>
<td>24,000</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55,000</td>
<td></td>
</tr>
<tr>
<td>T101</td>
<td>lgG1</td>
<td>pan-T cell</td>
<td>65,000</td>
<td>22, 23</td>
</tr>
<tr>
<td>OKT11</td>
<td>lgG1</td>
<td>E rosette receptor, pan-T cell</td>
<td>50,000</td>
<td>24</td>
</tr>
<tr>
<td>3A1</td>
<td>lgM</td>
<td>T cells</td>
<td>41,000</td>
<td>25</td>
</tr>
<tr>
<td>MCS-2</td>
<td>lgG1</td>
<td>Myeloid cells and monocytes</td>
<td>160,000†</td>
<td>26</td>
</tr>
</tbody>
</table>

Comparisons of the specificities of the MoAbs utilized with those of other MoAbs may be found in the report of the First International Workshop on Leukocyte Differentiation Antigens.27

*S. Pirruccello and T.W.L.B. (unpublished data).
†J.J. Griffin (personal communication).

MATERIALS AND METHODS

Marker analyses were performed in 90 adults with ALL. All patients were more than 16 years of age and were referred for phenotype determinations as part of a Cancer and Leukemia Group B adult ALL treatment protocol (#8011). Marker studies were performed on specimens obtained prior to the administration of induction therapy with vincristine, prednisone, daunorubicin, L-asparaginase, and intrathecal methotrexate.16 Clinical evaluations were performed as described previously.17 Pretreatment specimens from 116 patients were received for evaluation. Specimens were inadequate for phenotype determination in 20 cases (cells not viable, insufficient cells or low blast count). Six additional patients had incomplete marker analyses, were CALLA T and could not be classified as BA-1 and/or MCS-2. Evaluations were not performed. Blast cells for phenotype determination were isolated from heparinized peripheral blood and/or bone marrow aspirates by standard Ficoll-Hypaque density gradient centrifugation.18 The MoAbs used for phenotype determination are described in Table 1. Reactivity with murine MoAbs was determined by indirect immunofluorescence staining procedures and flow cytometry, as previously described.29 Conventional assays for terminal deoxynucleotidyl transferase (Tdt), E rosette formation (E), and surface immunoglobulin (sIg) were performed as described previously.30 The criterion for immunologic marker positivity was expression of the marker by at least 20% of the blast cell population. Complete marker profiles were not possible in all cases because of an insufficient number of cells.

Leukemic cells were evaluated by standard cytochemical assays as described30 for periodic acid Schiff’s stain (PAS), Sudan black B (SBB), peroxidase (PX) and a-naphthyl acetate esterase (a-NAE). Wright’s-Giemsa stained smears were also evaluated, and cases were classified according to the French-American-British (FAB) criteria.30 Statistical analyses were performed utilizing routine methods. Differences between phenotypic groups in leukocyte counts and age at study entry were evaluated by the two-sided Wilcoxon rank sum test. Comparisons of the incidence of other clinical parameters were evaluated by χ² analyses, with P values calculated as previously described.31 Demonstration of statistically significant P values for contingency tables comparing all phenotypic groups preceded comparisons between individual phenotypic groups.

RESULTS

Four major immunologic groups of adult ALL were identified on the basis of the expression of B-cell, CALLA, T-cell (T) and myeloid antigens (Table 2). The majority of patients had B lineage ALL (BA-1 T or CALLA T). Eleven of these cases were not tested for BA-1 reactivity and had CALLA T marker profiles. Inclusion of these cases in the B lineage ALL group is justified by our findings of BA-1 positivity in all CALLA T cases (38 patients) and is supported by the observation of Ig gene rearrangements, implying B cell origin, in ALL patients with CALLA T phenotypes.13 No cases of sIg B cell ALL were unequivocally demonstrated. Thus, the B lineage group was comprised of 49 cases previously termed “common” ALL (CALLA T).34 Plus an additional group of nine patients with BA-1 CALLA T marker profiles. The three remaining groups contained roughly equivalent numbers of patients and were defined as follows: T lineage ALL (T BA-1 MCS-2), unclassified ALL (BA-1 MCS-2 CALLA T) and myeloid antigen ALL.

Table 2. Major Immunologic Groups of Adult ALL

<table>
<thead>
<tr>
<th>Group</th>
<th>Defining Surface Markers*</th>
<th>No. of Cases</th>
<th>Total Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lineage ALL</td>
<td>BA-1 T or CALLA T</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>T-lineage ALL</td>
<td>T BA-1 MCS-2</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Unclassified ALL</td>
<td>BA-1 MCS-2 CALLA T</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Myeloid antigen ALL</td>
<td>MCS-2 CALLA T</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous ALL</td>
<td></td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

*T, T cell antigens defined by reactivity with either T101 or OKT11 MoAbs.
Cases with BA-1 MCS-2 CALLA T marker profiles were termed unclassified ALL. The predominant phenotype in this group was Ia 'BA-2'. Negative results were obtained for all of the other markers evaluated, with the exception of Tdt, which was positive in 67% of the cases studied.

Cases of ALL that were MCS-2 'CALLA' T were designated myeloid antigen ALL. All cases tested were Ia 'BA-1'. The majority of cases were Tdt and BA-2'. 3A1 positivity was observed in two of four cases evaluated for this marker. Five of these myeloid antigen positive cases had L2 type ALL by morphologic criteria. Tdt was positive in two of these cases, while a third case exhibited coarse PAS block positivity typical of ALL. Cells from the two remaining L2 patients were negative for both Tdt and PAS. All of the L2 cases were negative for either SBB or PX stains. The sixth patient in this group had a "biphenotypic" leukemia, and two distinct cell types were identified by morphologic evaluation (L2 and M4 populations). Leukemic cells from this patient were Tdt negative and exhibited fine granular PAS staining with approximately one-third SBB positive cells.

Correlation of the major phenotypic groups with presenting clinical features are shown in Table 4. Individuals with myeloid antigen ALL tended to be older than patients in the other groups. T lineage ALL cases were characterized by male predominance, high presenting WBC, and increased incidence of mediastinal mass. Unclassified ALL patients also had elevated presenting leukocyte (WBC) counts. The differences in the age of myeloid antigen ALL patients, and in the presenting WBC and incidence of mediastinal mass in T lineage ALL were statistically significant when compared to distributions in the CALLA' B lineage ALL group. No statistically significant differences in the incidence of presenting lymphadenopathy, hepatomegaly, or splenomegaly were identified between the major phenotypic groups.

While it is too early to correlate marker profiles with

![Fig 1. Marker expression in major immunologic groups of adult ALL.](image)

(MCS-2 'CALLA T'). Six patients had unusual marker profiles (miscellaneous ALL), and their marker data are considered separately.

The frequency of expression of the markers evaluated within each of the four major groups of adult ALL are shown in Fig 1. In the B lineage group (BA-1 'T' or CALLA 'T'), the predominant phenotype was Tdt 'Ia 'BA-2' and 84% were CALLA'. All cases tested were MCS-2 and 96% were BA-2'.

In T lineage ALL (T 'BA-1 'MCS-2'), all cases tested were either T101' (83%) or OKT11' (82%), and 87% were 3A1'. Less than a third of the cases evaluated were E rosette', and the majority were BA-2'. CALLA and Ia positivity were observed in 42% of cases. In four of five Ia' cases, greater than 50% of the blasts were Ia' and expressed T cell antigens. The remaining patient had 32% Ia' cells with greater than 90% T101'OKT11' blasts. In the CALLA' T-ALL patients, the degree of CALLA positivity was at least fourfold greater than the upper limit normal value of 10% reported for normal bone marrow.22 Thus, CALLA or Ia antigens were expressed by the leukemic T cells in these cases, and positivity for these antigens was not an artifact of residual normal bone marrow cells. Marker profiles in T lineage ALL were extremely heterogeneous and 12 distinct phenotypes were observed in the 12 patients evaluated (Table 3).

Table 3. Phenotypes in Adult T Lineage ALL Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>T101</th>
<th>OKT11</th>
<th>3A1</th>
<th>E</th>
<th>Tdt</th>
<th>Ia</th>
<th>CALLA</th>
<th>BA-1</th>
<th>BA-2</th>
<th>MCS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>-</td>
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<td>10</td>
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<td>ND</td>
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<td>+</td>
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<tr>
<td>11</td>
<td>+</td>
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</table>

ND, not done.
remission duration or survival, data on induction responses for the major groups of adult ALL are also depicted in Table 4. The percentage of patients achieving complete remission ranged from 33% (two of six) for the myeloid antigen ALL group to 100% (nine of nine) for patients with CALLA B lineage ALL. Sixty-five percent of CALLA B lineage ALL (30 of 46) patients achieved a complete remission. The increased incidence of complete remission induction responses for the CALLA B lineage ALL group was statistically significant (P < .05).

Six patients (miscellaneous ALL) had marker data that were difficult to classify. These rare cases either expressed unusual marker profiles or the evaluation of MoAb reactivity was problematic, because the percentage of positive cells was either just above or just below the cut-off value for positivity. Two patients were CALLA'MCS-2', and another case was BA-1'T'. An additional patient was CALLA'3A1'T with equivocal MCS-2 positivity, and two cases expressed T'MCS-2'3A1' marker profiles.

**DISCUSSION**

The present study extends previous investigations utilizing conventional assays and MoAbs in the characterization of ALL. Four major groups of adult ALL were identified on the basis of reactivity with MoAbs directed against B cell, CALLA, T cell, and myeloid antigens. The most common group was B lineage ALL (BA-1'T or CALLA'T). The remaining groups were observed less frequently and were comprised of patients with T lineage ALL (T'BA-1'MCS-2'), unclassified ALL (BA-1'MCS-2'CALLA'T') and myeloid antigen ALL (MCS-2'CALLA'T').

In contrast to these earlier investigations however, application of MoAbs to B cell and myeloid antigens unmasked the heterogeneity of patients with the previously "unclassified" CALLA T phenotype, identifying subgroups with distinctive clinical features. Patients with myeloid antigen ALL (MCS-2'CALLA'T') were older at presentation, and only two of six cases achieved a complete remission after induction therapy. Leukemic cells from these patients had morphologic and cytochemical features consistent with ALL. It is presently unclear whether these myeloid antigen-positive cases represent variant forms of ALL or "true" cases of acute myelogenous leukemia (AML) with unusual morphologic and cytochemical characteristics, as previously described by Tatsumi et al. All patients (nine of nine) with BA-1'CALLA'T phenotypes responded to induction therapy with a complete remission, and these cases had similar presenting clinical features as patients with CALLA'T' marker profiles. In agreement with previous reports describing T cell ALL, our T lineage ALL patients were characterized by male predominance, elevated leukocyte counts, and increased incidence of an anterior mediastinal mass. Longer follow-up of a larger number of patients will be necessary to determine if these groups have prognostic significance for remission rate, remission duration, or survival and to substantiate the clinical correlations identified in the present investigation.

In the T lineage ALL group, the majority of cases were T101'OHT1'3A1' and less than a third were E'. Most E' and all E' cases tested were OKT11' (E rosette receptor antigen). These findings suggest that monoclonal antibody detection of this T cell marker is more sensitive than rosette-forming assays and corroborate previous studies where E' cases exhibiting features of T cell disease were identified by polyclonal or monoclonal antibodies directed against T cell antigens. In childhood T-ALL, the vast majority of cases
are Ia⁺ and the apparent reciprocal expression of Ia and T cell antigens has proven valuable in the identification of childhood T-ALL. This contrasts with our observation of Ia antigen positivity in 42% of adult cases expressing T cell antigens. These findings suggest that the T’Ia⁺ phenotype may be more common in adult ALL. Of the T cell markers evaluated, 3A1 was positive in the highest proportion of cases tested. However, 3A1 reactivity has been observed in some cases of AML (I.R., T.W.L.B., and J.M., unpublished data). Furthermore, Link et al have reported the absence of Ia antigen positivity in 42% of adult cases of AML (I.R., T.W.L.B., and J.M., unpublished data). These findings suggest that the T’Ia⁺ phenotype may be more common in adult ALL. Of the T cell markers evaluated, 3A1 was positive in the highest proportion of cases tested. However, 3A1 reactivity has been observed in some cases of AML (I.R., T.W.L.B., and J.M., unpublished data). Furthermore, Link et al have reported the absence of Ia antigen positivity in 42% of adult cases of AML (I.R., T.W.L.B., and J.M., unpublished data).

Thus, caution should be exercised in identifying T cell antigens as 3A1 in one of eighteen cases evaluated with acute nonlymphocytic leukemia. The higher incidence of p24 antigen expression by normal hematopoietic cells is conserved by their mabig-ual phenotype. The higher incidence of p24 antigen expression by normal hematopoietic cells is conserved by their mabig-ual phenotype. Assuming that patterns of marker expression by normal hematopoietic cells are conserved by their malignant counterparts, these findings are consistent with the hypothesis that Ia and p24 antigens are expressed prior to other differentiation antigens, and that expression of p24 is conserved during the early stages of committed differentiation along B lymphoid and T lymphoid pathways.

In B lineage ALL, all CALLA⁺ cases tested were BA-1⁺ and several CALLA BA-1⁺ BA-2⁻ cases were identified. These observations suggest the possibility that the BA-1 antigen is expressed prior to CALLA during normal B-lymphoid differentiation, consistent with the observations of Korsmeyer et al. Employing a similar panel of MoAbs, Kersey et al have evaluated blast cell phenotypes in childhood ALL. As observed in our study, the predominant phenotype was CALLA⁺ Ia⁺ BA-1⁺ BA-2⁻. In contrast to our observation in adults of the absence of p24 antigen expression in only 4% of BA-1⁺ cases, 18% of 38 BA-1⁺ childhood ALL patients had CALLA BA-1⁺ BA-2⁻ lymphoblasts. As the p24 antigen is not expressed by mature lymphoid cells, the CALLA BA-1⁺ BA-2⁻ phenotype may possibly represent an arrest at a later stage of B lymphoid differentiation occurring more frequently in childhood than adult ALL.

A theory of early lymphoid differentiation based upon the phenotypes identified in this investigation and the considerations discussed above is presented in Fig 2. In the proposed schema, differentiation proceeds from an Ia⁺ BA-2⁺ progenitor cell. Commitment to B lymphoid differentiation is associated with the acquisition of the BA-1 antigen followed by expression of CALLA and subsequently, loss of the p24 (BA-2) antigen. Commitment to T lymphoid differentiation is accompanied by the acquisition of T cell antigens. Further stages of T lymphoid differentiation are accompanied by the loss of CALLA, Ia, and p24 (BA-2) surface markers. The higher incidence of CALLA T phenotypes in adults and the more frequent occurrence of T’Ia⁺ CALLA BA-1⁺ BA-2⁻ phenotypes in childhood ALL may possibly be explained by a higher proportion of adult cases being arrested at earlier stages of lymphoid differentiation.

The hypotheses presented in Fig 2 are likely to be modified as these and other MoAbs are further applied to the evaluation of normal and malignant hematopoietic cells. Our findings suggest that these MoAbs may prove clinically useful in the characterization of adult ALL, enhance our knowledge of the origin and heterogeneity of acute leukemias, and further our understanding of normal lymphoid differentiation.

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