Adult T-cell acute lymphoblastic leukemia: biologic profile at presentation and correlation with response to induction treatment in patients enrolled in the GIMEMA LAL 0496 protocol

Antonella Vitale, Anna Guarini, Cristina Ariola, Marco Mancini, Cristina Mecucci, Antonio Cuneo, Fabrizio Pane, Giuseppe Saglio, Giuseppe Cimino, Agostino Tafuri, Giovanna Meloni, Francesco Fabbiano, Anna Recchia, Maria Grazia Kropp, Mauro Krampera, Nicola Cascavilla, Felicetto Ferrara, Antonio Romano, Patrizio Mazza, Claudio Fozza, Francesca Paoloni, Marco Vignetti, and Robin Foà

Between 1996 and 2000, 90 newly diagnosed adult patients with T-acute lymphoblastic leukemia (T-ALL) were registered in the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) Leucemia Acuta Limfoide (LAL) 0496 protocol. Cases were centrally processed for morphology, immunophenotype, cytogenetics, molecular biology, and multidrug resistance (MDR). Twenty-two patients were females and 68 were males. Four percent of cases were pro-T, 47% pre-T, 39% cortical T, and 10% mature T-ALL. Fifty-six percent of patients with pro-T + pre-T-ALL achieved complete remission (CR) compared with 91% for cortical + mature cases ($P = .002$). CD34 expression was associated with a significantly lower CR rate: 54% versus 84% ($P = .009$). Thirty-one (36.5%) of 85 patients had an abnormal karyotype, the most common abnormality (15%) being a partial del(6q). The cytogenetic profile did not impact on CR achievement. MDR1 function, present in 26% of cases, correlated significantly with CR achievement ($P = .004$). A highly significant ($P = .001$) difference in CR rate was observed between patients who did not express the CD13/CD33/CD34 antigens and who were MDR functionally negative (96%) compared with patients positive for at least one of these markers (57%). Multivariate analysis showed an impact on CR achievement for CD33 expression and MDR1 function. An extensive biologic workup of adult T-ALL cases at presentation is recommended in order to design tailored therapeutic strategies aimed at improving CR rates. (Blood. 2006;107:473-479)

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Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the proliferation of lymphoid blast cells but represents indeed a heterogeneous group of diseases that vary with respect to the morphologic, cytogenetic, molecular, and immunologic features of the neoplastic cells. A progressive understanding of the biologic and genetic characteristics of ALL has not only improved our knowledge of leukemogenesis but also allowed us to identify different prognostic subgroups with specific molecular and cellular features. It is well established that the malignant clones in patients with ALL are characterized by the expansion of lymphoid progenitor cells blocked at early stages of B- or T-lymphocyte ontogeny. While cells from the majority of patients express B-lineage–associated antigens, T-ALL accounts for approximately 20% to 25% of patients. T-ALL has clinical, immunologic, cytogenetic, molecular, and genomic features that are distinct from those of B-lineage ALL.1-5 Although many reports,9-11 have generally described an unfavorable outcome for patients with T-lineage ALL, both in children and in adults, more recent studies have suggested an improved outcome through the use of highly intensive treatment protocols.4,12-14 These less unfavorable results have motivated attempts to identify subgroups of patients within T-ALL who may exhibit a more or less favorable response to treatment.

Only a few studies have analyzed the presentation features of relatively large series of adult patients with T-ALL in relation to the response to treatment and complete remission (CR) induction.1,3,15 In the present work, we have investigated the clinical and biologic features of 90 adult patients with T-ALL at diagnosis. Our analysis...
was performed in the context of the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) Leucemia Acuta Limfoide (LAL) 0496 protocol. This prospective, multicenter study enrolled a large series of uniformly treated adult ALL patients and required a central handling of fresh samples at presentation. Taking advantage of this overall framework, we uniformly analyzed a large series of patients with T-ALL and correlated their characteristics at diagnosis with the response to induction treatment.

### Patients, materials, and methods

#### Patients

Between October 1996 and July 2000, 90 adults with newly diagnosed T-ALL were registered in the GIMEMA LAL 0496 protocol (Figure 1), which is derived from the ALLVRS89 regimen12 and included patients aged 14 to 60 years with a diagnosis of ALL, with the exclusion of L3 B-ALL. The study was approved by the Institutional Review Board of the Department of Cellular Biotechnologies and Hematology, University “La Sapienza” of Rome. The protocol design has been described elsewhere.17 Informed consent was provided according to the Declaration of Helsinki and signed by all patients. All cases entered in the protocol were analyzed through a central handling of the samples at presentation and were all investigated for morphology, immunophenotype, cytogenetics, molecular biology, and multidrug resistance (MDR). Diagnosis of T-ALL was made according to the morphologic and cytochemical criteria of the French-American-British (FAB) classification.18

#### Immunophenotype

The immunophenotype of the 90 patients was performed by the referring centers on bone marrow or peripheral blood samples at presentation according to a predefined diagnostic panel of reagents. The reactivity with fluorescent conjugated monoclonal antibodies directed against lymphoid and myeloid associated antigens (CD20, CD3, CD2, CD5, CD7, CD13, CD33, CD14) was evaluated on the surface of leukemic cells. The intracytoplasmic Ig chain, CD3, CD79a, and myeloperoxidase antigens, as well as nuclear terminal deoxynucleotidyl transferase (TdT) staining, were evaluated by fluorescent-conjugated monoclonal antibodies after fixation and permeabilization of leukemic cells. Marked cells were analyzed using a flow cytometer (Becton Dickinson, San Jose, CA). The GIMEMA biologic committee reviewed the results. The surface markers were considered positive when 20% or more of the blasts expressed the antigen; intracytoplasmic positivity was defined on the basis of 10% or more reactive blasts.

#### Cytogenetic analysis

Metaphases from bone marrow short-term cultures were prepared in a single laboratory according to standard methods and GTG-banded chromosomes were classified following the International System for Human Cytogenetic Nomenclature.19 A minimum of 10 GTG-banded metaphases was required to consider the case evaluable. Three referral laboratories (Department of Cellular Biotechnologies and Hematology, University “La Sapienza,” Rome; Department of Biomedical Science Hematology Unit, University of Ferrara; Hematology and Bone Marrow Transplantation, University of Perugia) performed the cytogenetic analyses at diagnosis. Bone marrow samples for cytogenetic evaluation were obtained before starting therapy. The GIMEMA cytogenetic committee reviewed all cases.

#### Molecular investigations

The presence of different fusion transcripts (E2A-PBX1, BCR-ABL, ALL1-AF4, TEL-AML1) was detected by reverse transcriptase-polymerase chain reaction (RT-PCR). RNA extractions and the subsequent reverse transcription of RNA were carried out as previously described.20 We also studied CDKN2B/CDKN2A deletions by Southern blot analysis, as previously described.21 All of these analyses are part of the investigatory workup for all adult ALL cases entering the ongoing GIMEMA trials and are carried out in 3 referral laboratories (Department of Cellular Biotechnologies and Hematology, University “La Sapienza,” Rome; Department of Clinical and Biological Sciences, S. L. Gonzaga Hospital, Orbassano, University of Turin; Department of Biochemistry and Medical Biotechnologies, University Federico II of Naples).

#### Multidrug resistance

MDR1 expression and function were assessed in the same laboratory (Department of Cellular Biotechnologies and Hematology, University “La Sapienza,” Rome) by 2 cytometric tests, as already described.17 MDR1 expression was measured by flow cytometric detection of P-gp expression that was considered positive with a D value (Kolmogorov-Smirnov statistic test) of .05 or greater; MDR1 function was investigated using the rhodamine-123 (Rhd-123) efflux test that was considered positive for values of 1.10 or greater.

#### Statistical analysis

Statistical analysis was performed taking into account sex; age; white blood cell (WBC) count; hemoglobin (Hb) level; platelet (Plt) count; presence or absence of hepatomegaly, splenomegaly, mediastinal mass, and lymphadenopathy; presence or absence of CD10, CD13, CD33, and CD34 antigens; cytogenetics; molecular biology; and MDR. The cutoff levels of age, leukocytosis, anemia, and thrombocytopenia used for statistical comparison were derived from the median values of our data and earlier studies that established significant correlations of these values with patient survival.12,14,15 The characteristics of the patients and their response to treatment were compared by chi-square test and Fisher exact test for univariate analysis. All tests were 2 sided, accepting P less than .05 as indicating a statistically significant difference. Logistic regression using the backward method was performed to examine and check for risk factors affecting CR rate. The SAS software (SAS Institute, Cary, NC) release 8.02 was used for the analysis.

#### Results

Of the 416 patients registered in the GIMEMA LAL 0496 protocol, 90 (22%) had T-ALL. All were analyzed for their clinical and...
Table 1. Clinical-pathologic characteristics of 90 adults with T-ALL

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>26.6 (14.0-51.8)</td>
</tr>
<tr>
<td>M/F</td>
<td>68/22</td>
</tr>
<tr>
<td>Lymphadenopathy (%)</td>
<td>61 (70)</td>
</tr>
<tr>
<td>Splenomegaly, 2 cm or larger (%)</td>
<td>51 (57)</td>
</tr>
<tr>
<td>Mediaternal mass, chest X-ray (%)</td>
<td>40 (44)</td>
</tr>
<tr>
<td>Hepatomegaly, 2 cm or larger (%)</td>
<td>34 (38)</td>
</tr>
<tr>
<td>CNS (%)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Extrahematopoietic sites* (%)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

Laboratory data

- Blast count range, %
  - BM: 41-100
  - PB: 0-100
- Median WBC count, × 10^9/L (range): 48.2 (0.5-848.0)
- Median hemoglobin level, g/L (range): 108 (41-167)
- Median platelet count, × 10^9/L (range): 69.0 (3.3-310.0)

Morphologic features, FAB, n

- L1: 37
- L2: 45
- NA: 8

BM indicates bone marrow; PB, peripheral blood; and NA, not applicable.

*Kidney, skin, internal ear, and testis.

biologic characteristics. Of the 90 patients with T-ALL registered, 4
decreased treatment and 2 others failed to meet the eligibility
requirements; thus, 84 patients were eligible for treatment. How-
ever, only 78 patients were available for statistical analysis because
6 further patients were not evaluable for CR achievement.

Patient characteristics

Sex, age, WBC count, Hb level, Plt count, percentage of bone marrow
blasts, FAB classification, and clinical characteristics at presentation
are summarized in Table 1. Anemia (Hb level ≤ 100.0 g/L [10.0 g/dL])
was present in 40% of patients and thrombocytopenia (Plt
count ≤ 100 × 10^9/L) in 67% of patients. By univariate analysis
(Table 2), an impact on achievement of CR was found for sex
(Table 2). Univariate analysis on CR achievement
summarized in Table 1. Anemia (Hb level
and/or CD33, CD10

Table 2. Univariate analysis on CR achievement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
<th>CR %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤ 30 y vs &gt; 30 y</td>
<td>83 vs 63</td>
<td>.04</td>
</tr>
<tr>
<td>Sex</td>
<td>M vs F</td>
<td>84 vs 52</td>
<td>.004</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>+ vs −</td>
<td>71 vs 94</td>
<td>.06</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+ vs −</td>
<td>77 vs 77</td>
<td>NS</td>
</tr>
<tr>
<td>Mediaternal mass</td>
<td>+ vs −</td>
<td>74 vs 79</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+ vs −</td>
<td>74 vs 76</td>
<td>NS</td>
</tr>
<tr>
<td>WBC count</td>
<td>≤ 50 × 10^9/L vs &gt; 50 × 10^9/L</td>
<td>64 vs 87</td>
<td>.02</td>
</tr>
<tr>
<td>Hb level</td>
<td>≤ 100 g/L vs &gt; 100 g/L</td>
<td>78 vs 74</td>
<td>NS</td>
</tr>
<tr>
<td>Plt count</td>
<td>≤ 100 × 10^9/L vs &gt; 100 × 10^9/L</td>
<td>73 vs 78</td>
<td>NS</td>
</tr>
<tr>
<td>FAB</td>
<td>L1 vs L2</td>
<td>82 vs 71</td>
<td>NS</td>
</tr>
<tr>
<td>CD10</td>
<td>+ vs −</td>
<td>82 vs 73</td>
<td>NS</td>
</tr>
<tr>
<td>CD13 and/or CD33</td>
<td>+ vs −</td>
<td>57 vs 80</td>
<td>.08</td>
</tr>
<tr>
<td>CD34</td>
<td>+ vs −</td>
<td>54 vs 84</td>
<td>.009</td>
</tr>
<tr>
<td>Cytogenetic groups</td>
<td>Unsuccessful vs normal vs abnormal</td>
<td>83 vs 69 vs 66</td>
<td>NS</td>
</tr>
<tr>
<td>CDKN2B and/or CDKN2A</td>
<td>+ vs −</td>
<td>80 vs 73</td>
<td>NS</td>
</tr>
<tr>
<td>MDR1 expression</td>
<td>+ vs −</td>
<td>60 vs 83</td>
<td>.08</td>
</tr>
<tr>
<td>MDR1 function</td>
<td>+ vs −</td>
<td>46 vs 89</td>
<td>.004</td>
</tr>
</tbody>
</table>

*30% CD10, 24% CD13 and/or CD33, 34% CD34.
†Pseudodiploid, 19/31 (61%); hyperdiploid (47-50 chromosomes), 11/31 (36%); hyperdiploid (> 50 chromosomes), 1/31 (3%).

Immunophenotypic findings

The immunologic subtypes, defined according to the European
Group for the Immunological Characterization of Acute Leukemias
(EGIL) classification system, were as follows: 4% pro-T (stage I),
47% pre-T (stage II), 39% cortical-T (stage III), and 10% mature-T
(stages IV) (Table 3). The percentages of CR were 33%, 58%, 93%, and
80% for stages I, II, III, and IV, respectively. Since the number
of patients in each of the 4 categories was relatively small, we
arbitrarily clustered as immature T-ALL (51% of patients) stages I
and II, and as mature T-ALL (49% of patients) stages III and IV.
The correlation of these 2 groups with the achievement of CR
showed that the immature group had a significantly worse CR rate
than the mature group: 56% versus 91%, P = .002. Among the
patients with T-ALL tested for CD10, 30% expressed the antigen;
no statistical difference in terms of CR was recorded between the
CD10+ group and the CD10+ group (Table 2). Myeloid antigen
(MyAg) coexpression, CD13 and/or CD33, was examined and 24% of
cases tested positive for at least 1 of the 2 markers, more
frequently CD13 than CD33. CD13 was in fact documented in 8% of
cases, whereas CD33 was observed in 10% of cases; 4% of cases

Table 3. Biologic characteristics of 90 adults with T-ALL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunophenotype, %*</td>
<td></td>
</tr>
<tr>
<td>T-I (pro-T)</td>
<td>4</td>
</tr>
<tr>
<td>T-II (pre-T)</td>
<td>47</td>
</tr>
<tr>
<td>T-III (cortical-T)</td>
<td>39</td>
</tr>
<tr>
<td>T-IV (mature-T)</td>
<td>10</td>
</tr>
<tr>
<td>Cytogenetics, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Unsuccessful karyotype</td>
<td>25/85 (29.4)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>29/85 (34.1)</td>
</tr>
<tr>
<td>Abnormal karyotype</td>
<td>31/85 (36.5)†</td>
</tr>
<tr>
<td>Molecular biology, no. (%)</td>
<td></td>
</tr>
<tr>
<td>BCR-ABL†</td>
<td>1/90 (1)</td>
</tr>
<tr>
<td>NUP98-RAP1GDS1†</td>
<td>2/90 (2)</td>
</tr>
<tr>
<td>CDKN2B+ /CDKN2A+</td>
<td>16/62 (26)</td>
</tr>
<tr>
<td>MDR1, no. (%)</td>
<td></td>
</tr>
<tr>
<td>P-gp+ expression</td>
<td>16/68 (24)</td>
</tr>
<tr>
<td>P-gp+ function</td>
<td>14/54 (26)</td>
</tr>
</tbody>
</table>

NS indicates not significant.
coexpressed both markers. On the basis of the positivity for at least 1 of the 2 myeloid markers (CD13 and/or CD33), we stratified patients into 2 groups: a MyAg+ group and a MyAg− group. Comparison between the MyAg+ group and the MyAg− group showed a difference in terms of CR achievement, 57% versus 80%, which failed however to reach statistical significance ($P = .08$; Table 2). CD34 expression was found positive in 34% of the cases tested and this positivity had a significant negative effect on CR achievement: 54% versus 84%, $P = .009$ (Table 2).

Frequency of chromosomal abnormalities

Of the 90 patients with T-ALL, only 5 (5%) did not have a sample for cytogentic evaluation. Of the 85 patients analyzed, 25 (29.4%) had an unsuccessful cytogenetic evaluation (<10 metaphases). Of the 60 successfully karyotyped cases, a normal karyotype was found in 29 (48%). Of these, 11 (38%) had fewer than 20 metaphases available for analysis. Of the 31 patients (52%) with an abnormal karyotype, none were hypodiploid, 19 (61%) were pseudodiploid, 11 (35%) were hyperdiploid with 47 to 50 chromosomes, and only 1 was hyperdiploid with more than 50 chromosomes (Table 3). The most common chromosome abnormality in our series was partial del(6q), which was present as a single abnormality in 5 patients and associated to other abnormalities in 4; its incidence among the global evaluable karyotypes was 15%. The breakpoint region was determined in all cases; 7 showed a deletion that encompassed the 6q21-q23 regions, whereas 2 showed a breakpoint respectively distal to 6q23 and proximal to 6q21. The translocation t(10;14)(q24;q11) was present in 2 patients (3.3%); in 1 of 2, t(10;14) was associated with del(6q). One case presented the t(9;22)(q34;q11) translocation, confirmed by molecular analysis (BCR/ABL p210); one patient presented the t(4;11)(q21;CDKN2B) translocation, as recently described in detail by Meucci et al.23 Six patients presented complex karyotypes (>3 numeric and structural abnormalities) and 9 patients presented other singular aberrations. No statistical differences in terms of CR were documented among the unsuccessful cytogenetic group, the normal cytogenetic group, or the abnormal cytogenetic group.

Molecular results

Molecular analyses were performed in all 90 patients according to the investigatory workup for all adult ALL cases entering the ongoing GIMEMA trials. All patients, except 1, were negative for BCR/ABL rearrangement; 2 patients presented the NUP98-RAP1GDS1 fusion.

We also investigated the CDKN2B and CDKN2A status in 62 patients, and a deletion of CDKN2B and/or CDKN2A was observed in 26% of cases (Table 3). We found no correlation between CDKN2B and/or CDKN2A gene status at diagnosis and the rate of CR (Table 2).

MDR results

MDR was evaluated as expression and function (Table 3). In 4 cases, MDR1 positivity was coupled to CD34 positivity and this combined expression was negatively associated with response to treatment since all 4 patients failed to obtain CR. In univariate analysis, patients who were positive for MDR1 expression had a lower CR rate, even if this difference did not reach statistical significance (Table 2); MDR1 function, in contrast, showed a significant correlation with achievement of CR: 46% for MDR1+ cases versus 89% for MDR1− cases ($P = .004$).

Statistical analysis

Univariate analysis was performed to evaluate the impact on achievement of CR of sex; age; WBC count; Hb level; Plt count; FAB; presence or absence of hepatomegaly, splenomegaly, mediastinal mass, and lymphadenopathy; presence or absence of the CD10, CD13, CD33, and CD34 antigens; cytogentic; molecular biology; and MDR expression and function (Table 2). The upshots of these univariate analyses have been reported. On the basis of these results, a multivariate analysis, which included both “clinical” and “biologic” data, was performed. The clinical data were age, sex, WBC count, and lymphadenopathy. The biologic data were CD13, CD33, CD34, and MDR1 as function. The results showed an impact on achievement of CR only for CD33 expression (odds ratio [OR], 0.062; confidence interval [CI] 95%, 0.003-1.172; $P = .063$) and MDR1 as function (OR, 0.068; CI 95%, 0.010-0.438; $P = .0047$). In line with the results of univariate and multivariate analyses, we arbitrarily divided patients with T-ALL into 2 groups on the basis of the presence or absence of CD13 and/or CD33, CD34, and MDR1 as function. Sixty patients were evaluable for these features, and the comparison of the 2 groups (MyAg+−, CD34+−, MDR+− [62%] versus MyAg−, CD34−, MDR− [38%]) showed a highly significant difference in terms of CR achievement (57% vs 96%; $P < .001$).

Discussion

The prognosis of adult patients with T-ALL remains poor and early indicators of disease outcome would be particularly valuable for the design of new treatment strategies. Critical to the realization of this approach is the accurate assignment of individual patients to specific risk groups. The aim of the present study was to extensively define the biologic features of a large series of adult T-ALL cases enrolled in the multicenter GIMEMA 0496 protocol and uniformly characterized at presentation and to correlate them with the response to induction therapy. When classic presentation criteria (age, sex, WBC count, tumor mass) were analyzed, we could confirm previously published data indicating that T-ALL occurs more frequently in males younger than 30 years of age and is usually accompanied by a high WBC count and tumor mass. Univariate analysis showed an influence on achievement of CR for sex (males doing better), age ($\leq 30$ years), WBC count ($\leq 50 \times 10^9/L$), and lymphadenopathy but not for Hb level, Plt count, bone marrow findings, mediastinal mass, splenomegaly, and hepatomegaly.

A number of biologically defined risk factors have been considered. We stratified our 90 adult T-ALL cases into 4 maturational groups according to the EGIL classification, and the percentage of patients achieving remission was significantly lower for those with T-ALL blocked at the earliest maturational stage (pro–T- and pre–T-ALL). These results extend earlier observations suggesting that the immature phenotype may be associated with lower CR rate. Boucheix et al reported that CD10+ T-ALL had a higher likelihood of achieving CR than CD10− T-ALL cases; in our series, the expression of CD10 had no impact on CR achievement. The clinical significance of the presence of MyAg’s on the leukemic cells has been widely debated. While different investigators have associated the coexpression of MyAg’s with an adverse prognosis for patients with T-ALL, others have found similar outcomes. In our series, patients were classified as MyAg+ or MyAg− on the basis of the positivity for at least 1 of the 2 myeloid
markers CD13 or CD33. There is no significant difference in response to induction treatment, with a CR rate of 57% for the MyAg+ group and of 80% for the MyAg− group (P = .08). The prognostic significance of CD34 expression is also controversial,30,31 In our series, a significant difference in the rate of CR, 54% versus 84%, was observed between CD34+ and CD34− patients. Overall, the presence of MyAg’s and/or of the CD34 antigen identified a group of patients with T-ALL with an inferior response to induction therapy.

T-ALL has been associated with a normal karyotype in 30% to 40% of cases32-34 and our results are in line with these data. One large study found t(10;14), not t(11;14) as observed in childhood T-ALL,5 to be the most frequent translocation in adult T-ALL.52; in our series, only 2 patients presented a t(10;14)(q24;q11) and none a t(11;14). It has been reported that deletions of the long arm of chromosome 6 (6q) have a preferential association with T-ALL in adult patients.32,33 Indeed, half of del(6q) patients identified in the GIMEMA LAL 0496 protocol had T-ALL compared with 20% for patients without a del(6q) (P < .001). Thus, del(6q) represents the single most common chromosome abnormality in our T-ALL series (15%) and even if no differences have emerged in previous reports between cases carrying the anomaly as isolated change and cases with del(6q) plus other cytogenetic aberrations, in our patients the presence of del(6q) alone was associated with an unfavorable prognosis.35 One patient presented a t(9;22)(q34;q11), an event rarely associated with T-ALL and with an unclear clinical significance.36-38 One patient presented a t(4;11)(q21;CDKN2B), with proven fusion between NUP98 and RAP1GDS1.23,39 This new specific genetic change is present in 2% of our series of patients with T-ALL, since another patient with the same type of molecular fusion was documented in a retrospective analysis.40 The clinical significance of this molecular rearrangement is at present not defined. Analysis of the impact of karyotype on treatment response failed to document any significant difference in terms of CR among the various cytogenetic groups (unsuccessful, normal, and abnormal). Overall, the types and frequencies of chromosomal abnormalities occurring in B- and T-lineage ALL are markedly different, and the contrast between the prognostic impact of karyotype in B-cell ALL22,33,41 compared with its relative lack of importance in T-ALL is striking.

Previous studies have shown that the incidence of CDKN2B/CDKN2A deletions is higher in T-ALL than in B-lineage ALL,21,42 and their clinical significance has been debated.21,43-45 We confirm that CDKN2B and CDKN2A are frequently deleted in T-ALL (26%); on the basis of our results, the alterations of CDKN2B/CDKN2A alone are not prognostically significant in T-ALL at the time of diagnosis, since no relationship was observed between gene status and rate of CR.

Another potential factor responsible for the poor response to chemotherapy is the presence of the MDR phenomenon. Only few time of diagnosis, since no relationship was observed between gene expression/function and treatment response or patients’ follow-up chemotherapy is the presence of the MDR phenomenon. Only few studies have shown that the expression of MDR1 protein. Interestingly, induction treatment failed in all patients who coexpressed MDR1 and CD34; this unfavorable association has been previously reported, particularly in AML patients51,52 and, to a lesser extent, in ALL patients.53,54 The possibility of identifying at diagnosis a subgroup of MDR1+/CD34− ALL patients with very poor prognosis warrants further investigations. Conversely, the rate of CR for patients in whom the leukemic cells did not express CD13, CD33, and CD34 and were MDR1 functionally negative was 96%.

Despite the improved outcome reported over the last decade, the overall prognosis of adult T-ALL remains poor.14 Thus, the identification of prognostically distinct subgroups of patients is essential in order to recognize at presentation patients with T-ALL who may witness a different likelihood of response to treatment. Our results show that the level of maturation of the blasts, as well as the expression of MyAg, CD34, and MDR1 as function, have a significant impact on response to treatment and CR achievement. Based on these findings, an extensive biologic workup of adult T-ALL cases at diagnosis, including also the study of gene expression profiling,7 is nowadays warranted in order to identify prognostically distinct subgroups of patients. A broad, uniform, and integrated biologically based prognostic stratification of patients T-ALL at presentation may in fact open the way to the design of tailored and risk-adjusted therapies, as is gradually becoming the case for B-lineage ALL.

Acknowledgment

The authors are grateful to the GIMEMA group for cooperation in this study.

Appendix


References


42. Hebert J, Cayuela JM, Berkeley J, Sigaux F. Candidate tumor-suppressor genes MTS1 (CDKN2A/INK4A) and MTS2 (CDKN2B/INK4B) display frequent homozygous deletions in primary cells from T- but not from B-cell lineage acute lymphoblastic leukemias. Blood. 1994;84:4038-4044.


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