Leukaemia Section

Review

11q23 rearrangements in childhood acute lymphoblastic leukemia

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Identity

Note

Clinical aspects of 11q23 abnormalities in childhood acute lymphoblastic leukemia (ALL) are herein described.

Clinics and pathology

Disease

Childhood acute lymphoblastic leukemia (11q23)

Note

Acute lymphoblastic leukemia (ALL) in infants is a clinically distinct entity from that diagnosed in older children. Infant ALL, which represents 3% of all cases of childhood ALL, is clinically aggressive and strongly associated with a poor prognosis. As mentioned below, leukemic cells in infants show preferential involvement of 11q23 chromosomal abnormalities / MLL gene rearrangements.

Phenotype/cell stem origin

Leukemic cells with 11q23 abnormalities, which include MLL gene rearrangements, are usually not hyperdiploid, have an early pre-B cell immunophenotype, and express myeloid antigens but not CD10. A few studies have found a strong association between 11q23 abnormalities and the expression of the human homolog of the rat chondroitin sulfate proteoglycan NG2. Therefore, the common immunophenotypes are CD19+, CD10-, CD15+, and/or CD65+, NG2+.

Etiology

There is strong molecular evidence that 11q23 abnormalities in infants with ALL occur in utero. The 11q23 band/MLL gene has an important role in normal hematopoietic growth and differentiation. Abnormalities in this region can occur very early in hematopoietic stem cell development. Indeed, in utero exposure to natural or synthetic substances that inhibit topoisomerase II (e.g., genistein, catechins, flavonoids) may result in acute leukemia. It has been suggested that rearrangement of the MLL gene leads to the inhibition of apoptosis and leukemogenesis.

Epidemiology

Depending on the method of detection, the incidence of 11q23 abnormalities among infants with ALL ranges from 60% to 80%. Among children who are older than 1 year and have ALL, the incidence of MLL gene rearrangements ranges from 4.5% to 5.7%. The t(4;11), one of the most common 11q23 abnormalities, occurs in 2% of children and adults with ALL.

The following information was obtained from 2 published reports of a multinational collaborative study of 497 pediatric patients with 11q23 abnormalities and ALL. In this study, some data for a few patients were unavailable.

Clinics

Children who have ALL and 11q23 abnormalities often experience organomegaly, high leukocyte counts, and involvement of the central nervous system (CNS) at the time of diagnosis.
11q23 rearrangements in childhood acute lymphoblastic leukemia

Raimondi SC

### Table 1. Frequency of five types of 11q23 abnormalities among three age groups of patients.

<table>
<thead>
<tr>
<th>11q23 abnormality</th>
<th>Total</th>
<th>Number of patients (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;1 year old</td>
</tr>
<tr>
<td>t(4;11)</td>
<td>252</td>
<td>149 (70)</td>
</tr>
<tr>
<td>t(11;19)</td>
<td>49</td>
<td>27 (13)</td>
</tr>
<tr>
<td>t(9;11)</td>
<td>19</td>
<td>8 (38)</td>
</tr>
<tr>
<td>t(11q23;V)</td>
<td>77</td>
<td>23 (11)</td>
</tr>
<tr>
<td>del(11q23)</td>
<td>94</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>491</td>
<td>212 (43)</td>
</tr>
</tbody>
</table>

Abbreviation: V, variable chromosome
*Percentage within the indicated age group.

### Table 2. The clinico-biological presenting features of 497 patients with ALL and 11q23/MLL rearrangement.

<table>
<thead>
<tr>
<th>11q23 abnormality</th>
<th>No. of Cases (%)</th>
<th>Median Age in Years (range)</th>
<th>Median WBC Counts, x 10⁹/L (range)</th>
<th>No. of patients with CNS involvement (%)*</th>
<th>No. of patients with T-lineage ALL (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;11)</td>
<td>256 (52)</td>
<td>0.65 (0.01-20.9)</td>
<td>224 (1-1400)</td>
<td>30 (12)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>t(11;19)</td>
<td>49 (10)</td>
<td>0.87 (0.03 - 16.7)</td>
<td>184 (3-1000)</td>
<td>5 (10)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>t(9;11)</td>
<td>20 ( 4)</td>
<td>1.46 (0.12 - 12.7)</td>
<td>51 (1-520)</td>
<td>4 (20)</td>
<td>0</td>
</tr>
<tr>
<td>t(11q23;V)</td>
<td>77 (15)</td>
<td>2.60 (0.02 - 15.1)</td>
<td>32 (2-1400)</td>
<td>8 (10)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>del(11q23)</td>
<td>95 (19)</td>
<td>5.34 (0.12 - 16.7)</td>
<td>14 (1-785)</td>
<td>5 (5)</td>
<td>13 (14)</td>
</tr>
</tbody>
</table>

Abbreviations: V, indicates a variable chromosome
*Fifty-two (11%) of 482 patients had CNS involvement.
**Forty (8.7%) of 459 patients had T-lineage ALL.

### Treatment

Because ALL in infants has distinctive biological characteristics and because infants have a high risk of leukemia recurrence, infants with ALL are usually treated on specifically designed protocols. Current intensified treatment approaches may offer better disease control in infants than do previously tested, less intensive approaches, but long-term outcome and toxicity are unknown.

Leukemic cells from infants with ALL are significantly more resistant to prednisone and L-asparaginase in vitro than are leukemic cells from older patients with ALL. However, leukemic cells in infants are highly sensitive to cytosine arabinoside (ara-C). These findings were incorporated into two cooperative treatment protocols for infants with ALL: the international Interfant-99 protocol and a protocol of the Children's Oncology Group in the United States. New therapeutic regimens are needed to cure infants with 11q23 abnormalities and high-risk ALL. Recent studies have shown high levels of FLT3 expression in patients with MLL rearrangements; therefore, inhibitors of FLT3 (a tyrosine kinase) may prove to be beneficial.

### Prognosis

The 11q23 abnormality/MLL gene rearrangement is generally associated with a high risk of treatment failure; in contrast, deletion or inversion of 11q23 is not. Although infants and adults with the t(4;11) are at higher risk of treatment failure, children aged 1 to 9 years appear to have a better outcome. For more details, see below.
Table 3. The impact of age and phenotype on the 5-year event-free survival (EFS) estimates for children with ALL and different types of 11q23 abnormality.

<table>
<thead>
<tr>
<th>Type of 11q23 abnormality</th>
<th>Age, Lineage</th>
<th>5-year EFS, % (s.e.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;11)</td>
<td>&lt;1 year, B lineage</td>
<td>19 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year, B lineage</td>
<td>42 (5)</td>
<td></td>
</tr>
<tr>
<td>t(9;11)</td>
<td>&lt;1 year, B lineage</td>
<td>38 (15)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year, B lineage</td>
<td>46 (14)</td>
<td></td>
</tr>
<tr>
<td>t(11;19)</td>
<td>&lt;1 year, B lineage</td>
<td>26 (8)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year, B lineage</td>
<td>46 (14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T lineage</td>
<td>88 (13)</td>
<td></td>
</tr>
<tr>
<td>t(11q23;variable)</td>
<td>&lt;1 year, B lineage</td>
<td>22 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year, B lineage</td>
<td>65 (7)</td>
<td></td>
</tr>
<tr>
<td>del(11)(q23)</td>
<td>&lt;1 year, B lineage</td>
<td>40 (22)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year, B lineage</td>
<td>73 (5)</td>
<td></td>
</tr>
</tbody>
</table>

**Cytogenetics**

**Cytogenetics morphological**

**t(4;11)**

The t(4;11) was the sole chromosomal abnormality in 200 (79%) of the 252 cases in which a t(4;11) was detected by conventional cytogenetics. The t(4;11) was observed in 41 cases that had other cytogenetic changes and in 11 cases that had variant translocations. In 4 cases, only molecular information (MLL-AF4+) was available.

The t(4;11) was present in 70% (149/212) of infants, 31% (58/188) of children aged 1 to 9 years, and 49% (45/91) of patients aged 10 years or more.

Infants with the t(4;11) had a worse outcome than did those who were older than 1 year (5-year event-free survival [EFS] estimates, 19% ± 3% vs. 42% ± 5%; P=0.0001).

The outcome of infants with the t(4;11) and poor prednisone response (n=12) was dismal (5-year EFS estimate, 0%), whereas infants with the same abnormality and a good prednisone response (n=11) had a slightly better outcome (5-year EFS estimate, 23% ± 12%; P=0.0005).

The outcome of infants who were younger than 3 months and had ALL and a t(4;11) was worse than that of infants who were older than 3 months and had ALL and the same chromosomal abnormality (5-year EFS estimates, 5% ± 5% vs. 23.4% ± 4%; P=0.0003).

A poor prednisone response also appeared to confer a poor outcome for ALL patients 1 year of age or older with a t(4;11) (5-year EFS estimate, 33% ± 16%). ALL patients in the same age group and with a t(4;11) and a good prednisone response had a 5-year EFS estimate of 80% ± 18% (P=0.077).

Leukocyte counts at initial examination had only a marginal prognostic impact for infants with t(4;11)-positive ALL and lacked significance for older pediatric patients in this genetic subgroup.

In a retrospective analysis of 256 patients with the t(4;11) treated between 1983 and 1995, allogeneic stem cell transplantation provided no greater benefit than did intensive chemotherapy alone.

**t(11;19)**

The t(11;19) was the sole chromosomal abnormality in 31 (63%) of the 49 cases in which the t(11;19) was detected. In 15 cases (31%) with a t(11;19), additional changes were present, and in 3 additional cases, variant translocations were observed.

The t(11;19) was found in 13% (27/212) of infants, 6% (12/188) of children aged 1 to 9 years, and in 11% (10/91) of children aged 10 years or more.

Patients who had this translocation and were younger than 1 year had a worse outcome than did older patients (5-year EFS estimates, 26% ± 8% vs. 64% ± 12%; P=0.003).

In the subgroup of infants with the t(11;19), age less than 6 months and female sex were associated with a poor treatment outcome; however, these findings from a multivariate analysis lacked statistical significance.

None of the 26 infants with a t(11;19) had T-cell ALL, but this type of ALL was present in 8 (38%) of the 21 children who were older than 1 year and had a t(11;19).

Of the patients with the t(11;19)(q23:p13.3) and the MLL-ENL fusion, those who had T-lineage ALL and were older than 1 year had a better outcome than did patients who had a t(11;19), were older than 1 year, and had B-lineage ALL (5-year EFS estimates, 88% ± 13% vs. 46% ± 14%, P=0.065). This finding confirmed previous observations.
t(9;11)
The t(9;11) was identified by RT-PCR only in 1 of 20 cases. Six (32%) of the other 19 cases had additional chromosomal changes; in 4 cases, a variant translocation was present. The t(9;11) was found in 3.8% (8/212) of infants, 5% (10/188) of children aged 1 to 9 years, and 1% (1/91) of patients aged 10 years or more. Age was not a predictor of outcome for infants with t(9;11)-positive ALL. Patients who had ALL and a t(9;11) and were younger than 1 year had a 5-year EFS estimate of 38% ± 15%, whereas those who had ALL and a t(9;11) and were older than 1 year had a 5-year EFS estimate of 46% ± 14% (P=0.27).

t(11q23;variable)
Of the 77 patients with a t(11q23;variable), 23 were infants. Southern blot analysis detected the abnormality in 6 infants. The t(11q23;variable) was found in 11% (23/212) of infants, 23% (44/188) of children aged 1 to 9 years, and 11% (10/91) of patients aged 10 years or more. The following recurrent chromosomal abnormali-ties were observed in 18 of the 23 infants: inv(11)(p15q23) (n=5), t(1;11)(p32;q23) (n=5), t(10;11)(p14-15;q23) (n=4), t(1;11)(q23;q23) (n=2) and t(10;11)(p13q23) (n=2). For patients younger than 1 year who had the t(11q23;variable), the 5-year EFS estimate was 22% ± 8%, whereas those older than 1 year who also had this abnormality had a 5-year EFS estimate of 65% ± 7% (P<0.0001).

del(11)(q23)
The del(11)(q23) occurred in 2% (5/212) of infants, 34% (64/188) of children aged 1 to 9 years, and 27% (25/91) of patients aged 10 years or more. Only 5 infants had a del(11)(q23), and their treatment outcome was worse than that of 89 older children with the same abnormality (5-year EFS estimates, 40% ± 22% vs. 73% ± 5%; P=0.05). Although patients with the del(11)(q23) were a very heterogeneous group, the National Cancer Institute-Rome risk criteria based on age and leukocyte count had prognostic significance: the 5-year EFS estimate was 64% ± 8% for patients with high-risk disease and 83% ± 6% for those with standard-risk disease (P=0.04).

The findings from the international collaborative study can be summarized as follows:
Only age at initial treatment had a significant effect on EFS estimates of pediatric patients with ALL and 11q23 abnormalities. Infants (n=212) uniformly fared worse than children aged 1 to 9 years (n=188) and those aged 10 years or more (n=91). Furthermore, when the two groups of older patients were further divided by type of 11q23 abnormalities, each group had a similar outcome. Irrespective of the 11q23 abnormality, infants had a worse treatment outcome than did older patients. Any category of 11q23 abnormality conferred a dismal outcome for infants, whereas in older patients the t(4;11) (n=103) and the t(9;11) (n=22) were associated with an outcome worse than that associated with other 11q23 changes. The t(4;11) and the t(11;19) were usually found in the youngest children, whereas the del(11)(q23) was typically detected in the oldest. The t(4;11) and the t(9;11) were rarely found in patients with T-lineage leukemia. Patients with the t(4;11) or the t(11;19) were most likely to belong to the high-risk group defined by the National Cancer Institute-Rome criteria, whereas those with the del(11)(q23) were the least likely.

T-lineage ALL was present in 40 (8.7%) of the 459 cases in which the leukemic cells’ immunopheno-type was known. CNS involvement was observed in 12% (52/430) of patients with 11q23 abnormalities. For patients with the t(4;11), any type of transplantation, including allogeneic transplantation of hematopoietic stem cells from an HLA-matched related or unrelated donor, was associated with significantly a worse disease-free survival estimate than was chemotherapy alone.

Cytogenetics molecular
Some MLL gene rearrangements are not detected by conventional cytogenetic methods. The commercially available dual-color MLL probe (Vysis, Inc., Downers Grove, IL, USA) allows FISH evaluation of derivatives of an MLL translocation in metaphase chromosomes and the splitting of the hybridizing probe’s signal in interphase nuclei. In rare instances, this probe detects not only the reciprocal translocation but also a deletion of at least 190 kb from the 3’ region of the MLL gene. Molecular cytogenetic methods have shown that the frequency of MLL gene rearrangements exceeds that of 11q23 translocations detected by conventional cytogenetic methods. In ALL cases in which deletions and inversions affect the 11q23 band (both types of abnormality are associated with favorable clinical features and prognoses), FISH should be done to determine whether a cryptic rearrangement of MLL is present. In a few cases, an 11q23 translocation involves genes other than MLL. Because the translocation partners for 11q23 are markedly heterogeneous, additional molecular methods are needed to further assess the MLL gene in patients with an 11q23 abnormality. Information from such assessments can then be used to better stratify treatment groups.

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