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REVIEW ARTICLE

Biology and Clinical Significance of Cytogenetic Abnormalities in Childhood Acute Lymphoblastic Leukemia

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IMPROVEMENTS in cytogenetic techniques have galvanized efforts to understand the biology of chromosomal changes in childhood acute lymphoblastic leukemia (ALL) and to identify specific alterations that predict treatment outcome. Seeker-Walker et al were the first to present evidence that the chromosome number (ploidy) of leukemic cells at diagnosis has prognostic significance in childhood ALL. Subsequent studies indicated that other cytogenetic findings, including the presence of a chromosomal translocation, have an adverse effect on prognosis. In addition to their clinical importance, cytogenetic abnormalities have provided the focus for molecular studies designed to elucidate the mechanisms of lymphoid cell transformation and aberrant regulation of leukemic cell growth. This review addresses the biologic and prognostic importance of leukemic cell chromosomal abnormalities in childhood ALL, emphasizing new information from molecular genetic studies and the impact of recent improvements in chemotherapy.

FREQUENCY OF CLONAL ABNORMALITIES

Cytogenetic analysis of ALL was initially a difficult challenge because standard chromosome-processing techniques yielded fuzzy, ill-defined metaphases. With improved banding methods, investigators have identified clonal chromosomal abnormalities in 55% to 80% of cases in most recent studies. Relying on a direct technique for preparing metaphase spreads, optimal sampling procedures, and short-term cultures in selected cases, Williams et al are now able to identify clonal chromosome abnormalities in over 90% of cases of ALL, a success rate comparable to that achieved with the high resolution technique of Yunis et al in acute nonlymphoblastic leukemia. Despite this advance, one fourth of cases with a T-cell phenotype still lack detectable leukemic cell chromosomal abnormalities. Normal karyotypes are found most often in T lymphoblasts with cell surface features corresponding to early stages of normal T-cell development.

NUMERICAL CHROMOSOMAL ABNORMALITIES

The distribution of modal chromosome numbers in ALL is bimodal, with a major peak occurring at 46 (mainly pseudodiploid karyotypes), a smaller peak at 55, and a hiatus at 50. This pattern is characteristic of ALL and is not found in other types of leukemia. Several major ploidy groups have been identified in childhood ALL (Table 1).

Hyperdiploidy >50 chromosomes. Patients with >50 chromosomes per leukemic cell account for about one fourth of childhood ALL cases and have proved to have the most durable responses to treatment. This ploidy group can be reliably identified in an automated fashion by flow cytometric analysis of the amount of DNA in leukemic lymphoblasts. Its characteristics were poorly understood until recently because of the difficulty of studying such cases by standard cytogenetic techniques. Although any chromosome can be involved in trisomies, chromosome numbers 4, 6, 10, 14, 17, 18, 20, 21, and X are added most frequently; in fact, four copies of chromosome 21 can be found in some cases. We recently analyzed 134 cases with >50 chromosomes, finding a tight distribution of modal chromosome numbers around a median of 55 chromosomes. Structural chromosomal abnormalities, in addition to the gain of whole chromosomes, were found in 62% of cases; translocations were found in 20%.

The mechanism(s) underlying the preferential addition of certain chromosomes and the clustering of modal chromosome numbers around 55 is unknown. Compared with other karyotypic subgroups, hyperdiploidy >50 is significantly more frequent in early pre-B ALL (CD19+, CD5−, CD7−, cytoplasmic and surface immunoglobulin [lg] negative) and is associated with other established favorable prognostic features, including expression of CD10 (common ALL antigen, now identified as neutral endopeptidase) by leukemic blasts, lower leukocyte count, lower serum lactic dehydro-
genase level, white race, and age between 2 and 10 years (Table 2). Hyperdiploidy is notably absent in patients with a very young age, a clinical presenting feature known to be an independent predictor of a poor outcome.24–28 We have suggested that isochromosome 17q is an adverse cytogenetic feature within the hyperdiploid >50 subtype of childhood ALL.29 Later, we demonstrated that in the hyperdiploid >50 subgroup, patients with concurrent structural chromosomal abnormalities generally have a less favorable prognosis than those with only numerical abnormalities.23 It is noteworthy that hyperdiploid >50 cases with and without structural chromosomal abnormalities have similar presenting features and would not otherwise be distinguishable. Jackson et al30 correlated the presence of an extra chromosome 6 with improved prognosis among children with hyperdiploid ALL; however, their study included cases with hyperdiploid 47 to 50 that rarely had an added chromosome 6. Thus, the good prognosis reported for cases with an extra chromosome 6 may be explained by the close association of trisomy 6 with hyperdiploidy >50.

**Pseudodiploidy.** This is the largest cytogenetic subgroup in childhood ALL, characterized by a chromosome number of 46 per cell with structural abnormalities, mainly translocations. Numerical changes are seldom observed in pseudodiploid cases and are random with respect to the chromosomes involved.4 The initial leukemic cell burden tends to be large in pseudodiploid cases, as reflected by high leukocyte counts and elevated serum lactic dehydrogenase levels (LDH; Table 2).6,10,31 The early pre-B phenotype is less common among pseudodiploid cases.10 Although an excess of cases with L2 morphology has been reported within the pseudodiploid category,6,10 we have been unable to confirm this correlation. Contemporary programs of intensive chemotherapy have substantially improved treatment outcome in this subgroup,9 once associated with a very poor prognosis.1,5,6,10,16,20

**Hypodiploidy.** Fewer than 46 chromosomes per leukemic cell is a relatively uncommon finding in ALL, affecting only 3% to 9% of patients.23,30,31,32 Most of the cases (>80%) have a primary leukemic cell line with a modal chromosome number of 45. Chromosome 20 is lost most frequently, and in some cases a missing chromosome 20 may be the only abnormality.31 Hypodiploid cases have a high frequency of chromosomal translocations, comparable with that of pseudodiploid cases,31 and fare poorly despite intensive treatment.10,20,31,34 Hypodiploid cases can be further divided into three subgroups based on cytogenetic and clinical features: near-haploid, hypodiploid 30 to 40, and hypodiploid 41 to 45. Near-haploid ALL is a unique subgroup. Of the 20 cases reported in the literature,31,35–43 only one was found to have a structural chromosomal abnormality.36 Blast cells from these patients have nonrandom retention of two copies of chromosomes 8, 10, 14, 18, 21, and the sex chromosomes, and generally have a second hypodiploid line with a chromosome number double that of the near-haploid line.34 Most of the hypodiploid 30 to 40 and hypodiploid 41 to 45 cases have structural chromosomal abnormalities.31,34 As in the near-haploid group, chromosome 21 and the sex chromosomes are preferentially retained in these cases. The presenting clinical features of patients with hypodiploid ALL are similar to those seen in childhood ALL in general. Notable exceptions are the slight excess of females in near-haploid cases and the older median age of patients in the hypodiploid 30 to 40 group.34,43

**Hyperdiploidy 47 to 50 chromosomes.** This subset of patients comprises approximately 15% of children with ALL, who appear to have an intermediate prognosis.5,20,33 In a study of 31 cases, Williams et al14 found a nearly equal frequency of structural and numerical abnormalities, which were randomly distributed. Comparisons of karyotypes in cases with 47, 48, and 49 chromosomes failed to disclose any consistent patterns of abnormalities, and there were no similarities between this ploidy group and the group with 51 or more chromosomes. In a recent update, we found translo-

### Table 1. Frequency of Ploidy Groups in Childhood ALL Cases

<table>
<thead>
<tr>
<th>Ploidy Group</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near haploidy</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Hypodiploidy 30-40</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Hypodiploidy 41-45</td>
<td>6.0</td>
</tr>
<tr>
<td>Pseudodiploidy</td>
<td>41.5</td>
</tr>
<tr>
<td>Hyperdiploidy 47-50</td>
<td>15.5</td>
</tr>
<tr>
<td>Hyperdiploidy &gt;50</td>
<td>27.0</td>
</tr>
<tr>
<td>Near triploidy</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Near tetraploidy</td>
<td>1.0</td>
</tr>
<tr>
<td>Normal</td>
<td>8.0</td>
</tr>
</tbody>
</table>

See references 13, 15, 31, 34, 44, and 53.

### Table 2. Distribution of Presenting Features by Ploidy Group in Childhood ALL

<table>
<thead>
<tr>
<th></th>
<th>Hypodiploid</th>
<th>Pseudodiploidy</th>
<th>Hyperdiploid 47-50</th>
<th>Hyperdiploid &gt;50</th>
<th>Near Tetraploidy</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>5.0</td>
<td>6.0</td>
<td>5.4</td>
<td>3.8</td>
<td>8.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Median WBC (× 10^9/L)</td>
<td>12.7</td>
<td>31.6</td>
<td>11.1</td>
<td>6.6</td>
<td>8.2</td>
<td>38.3</td>
</tr>
<tr>
<td>Median LDH (U/L)</td>
<td>488</td>
<td>687</td>
<td>511</td>
<td>324</td>
<td>ND</td>
<td>670</td>
</tr>
<tr>
<td>% Nonwhite race</td>
<td>10</td>
<td>17</td>
<td>13</td>
<td>7</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>% FAB L1</td>
<td>84</td>
<td>86</td>
<td>88</td>
<td>90</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>% Chromosomal translocation</td>
<td>68</td>
<td>67</td>
<td>35</td>
<td>20</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Immunoexpression</td>
<td>% Early pre-B cell</td>
<td>61</td>
<td>51</td>
<td>72</td>
<td>81</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>% Pre-B cell</td>
<td>29</td>
<td>26</td>
<td>23</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>% T cell</td>
<td>10</td>
<td>23</td>
<td>5</td>
<td>3</td>
<td>47</td>
</tr>
</tbody>
</table>

See references 5, 15, 22, 31, 34, and 44.

Abbreviation: ND, not done.
cations in one third of the cases, a proportion intermediate between that of the hyperdiploid > 50 group and pseudodiploid or hypodiploid cases (Table 2). Preliminary observations suggested that the presenting clinical features of the hyperdiploid 47 to 50 cases do not differ from those of childhood ALL in general.

Near tetraploidy and near triploidy. Because of its rarity (1% of children with ALL) the prognosis of near-tetraploid cases is uncertain. In a recent study using cytogenetic and flow cytometric techniques, investigators of the Pediatric Oncology Group (POG) and St Jude Children’s Research Hospital identified 20 near-tetraploid cases among 1,971 children with newly diagnosed ALL.44 The modal chromosome number in these cases ranged from 82 to 94. Chromosome 21 was added in all evaluable cases and was found in more than four copies in five. Near-tetraploid lines appear to arise from endoreduplication, because paired chromosomes with the same rearrangements or deletions were found in some cases. Morphologically, these cases were more likely to have L2 blasts than those of other ploidy groups (Table 2). Moreover, the blast cell morphology of these cases is characterized by clumped chromatin and grooved nuclei or Rieder-cell formation, probably representing an attempt of the cell to accommodate the extra DNA.

Near-tetraploid cases were significantly more likely to have a T-cell immunophenotype (47%) and to occur in patients with an older age at diagnosis (median 8.6 years), as compared with children in other abnormal ploidy groups. Similarly, a T-cell phenotype was found in three of the six other near-tetraploid cases reported in childhood ALL; these patients had a median age of 11 years.18,45,46 Because of the associated T-cell phenotype and older age, near-tetraploid cases might be expected to have a poor treatment outcome. However, the prognostic significance of this finding is uncertain because of the small number of reported cases. Even less is known about near-triploid ALL (only seven childhood cases have been reported).44,49 It is uncertain whether the near-triploid cases should be considered a distinct clinical and biologic entity or whether they should be included with the other hyperdiploid > 50 cases.

Normal diploidy. The percentage of cases with an apparently normal diploid leukemia karyotype has varied widely among reported series, with most studies indicating an intermediate prognosis for this subgroup.5,10,39 As cytogenetic techniques have improved, the proportion of cases lacking clonal abnormalities has diminished; in our recent studies, only 8.6% of cases, half with a T-cell phenotype, were considered karyotypically normal.13,15 Most previously reported cases with this classification are now recognized to be pseudodiploid. Conceivably, all cases of ALL will prove to have one or more clonal chromosomal abnormalities, some of which are difficult to recognize by current techniques based on light microscopy. Some cases may have only submicroscopic genetic changes, requiring molecular approaches for detection. Normal karyotypes could also reflect dividing residual non-neoplastic marrow elements in cases in which the leukemic cells have a low mitotic fraction.

In the first Morphologic, Immunologic, and Cytogenetic (MIC) Workshop, two thirds of the ALL cases were found to have at least one nonrandom chromosomal abnormality,50 often in association with specific immunophenotypes. In 1987, 30 nonrandom structural abnormalities in ALL were recognized by the Ninth Human Gene Mapping (HMG) Conference51; six additional nonrandom structural abnormalities were described at a subsequent HMG workshop.52 The number of recurring structural chromosome abnormalities found in ALL clones will undoubtedly increase as more cases are studied. Among structural chromosomal abnormalities, specific translocations, most often involving reciprocal exchanges of DNA, are a prominent feature. Drs Dorothy Williams and Susana Raimondi have identified leukemic cell chromosome translocations in approximately 50% of cases of childhood ALL admitted to our center.13,53 Thus far, about half of these translocations have been shown to result from nonrandom. Table 3 lists some of the recurrent translocations, together with the associated leukemic cell immunophenotypes. Because of their unique clinical and biologic features, the most prominent specific chromosomal rearrangements will be discussed individually.

Philadelphia (Ph) chromosome. The 22q-chromosomal marker, first described by Nowell and Hungerford53 in 1960, has been shown by banding techniques to result from a balanced translocation, t(9;22)(q34;q11). Originally thought to be associated only with chronic myelogenous leukemia (CML), this translocation has since been identified in leukemic cells of 3% to 5% of children,45,54 and 15% to 25% of adults55,56 with ALL. Features closely associated with the presence of the Ph chromosome in childhood ALL are an older age at presentation, a high leukocyte count, French-American-British (FAB) L2 morphology, and a high incidence of central nervous system (CNS) leukemia.55,56 The distribution of major immunophenotypes in children with Ph+ ALL does not differ significantly from those with ALL in general.55,56 In contrast to CML involving a multipotential stem cell for both myeloid and lymphoid (B and T) cells,59,60 childhood ALL is a clonal disorder that usually affects a committed lymphoid progenitor of either T or B lineage.61 Interestingly, some cases of Ph+ ALL have also been shown to involve a pluripotent hematopoietic progenitor cell.62 Clinically, the distinction between Ph+ ALL and Ph+ CML in lymphoblastic crisis can be difficult, but certain differences emerge after chemotherapy-induced remission. The Ph chromosome is generally found in marrow cells from patients with Ph+ CML in hematologic remission, whereas the Ph chromosome rarely persists in remission bone marrow cells from patients with Ph− ALL.55,56

Results of recent studies have demonstrated that Ph+ ALL and Ph+ CML differ at the molecular level. In both ALL and CML with the t(9;22), the ABL gene is translocated from chromosome 9 to chromosome 22. The breakpoints on the long arm of chromosome 9 are variable and may occur over a distance of more than 100 kilobases (kb) within the ABL gene, upstream of the tyrosine kinase domain.63,64 In CML, the breakpoint on chromosome 22 generally lies within a well-defined 5.8-kb region of genomic DNA, known as the
breakpoint cluster region (bcr) or major breakpoint cluster region 1 (M-BCR-1). This region of chromosome 22 is within a gene called BCR (or PHL) that encodes a 160-Kd phosphoprotein with an associated serine/threonine kinase activity.55–60 The translocation results in a fusion of the BCR and ABL genes with production of a characteristic 8.0- to 8.5-kb messenger RNA (mRNA) and a 210-Kd hybrid protein.85–87 By contrast, in most cases of Ph+ ALL, the breakpoint on chromosome 22 occurs within the first intron of BCR, 40 kb upstream of the M-BCR-1. This new breakpoint cluster region in ALL has been variously called bcr 2 or m-BCR-1, which stands for minor breakpoint cluster region.69 The fusion gene created by the translocation encodes an mRNA of 6.5 to 7.0 kb, which is translated into a 185-Kd protein.70–74 Only occasionally does the BCR–ABL gene rearrangement of ALL result in a P210br-abl similar to that of CML.75

Both P210br-abl and P185br-abl proteins have identical elements derived from ABL, including the tyrosine kinase domain, but the latter lacks 501 internal BCR-derived residues. Both types of BCR–ABL fusion genes encode protein products that function as constitutively activated tyrosine kinases, which may be involved in aberrant intracellular signaling.75 Hematologic malignancies, including ALL and CML, were induced in mice after their bone marrow was infected with a retrovirus encoding P210br-abl.76 Recently, P185br-abl was shown to be more potent than P210br-abl in transforming both hematopoietic cells and fibroblasts, suggesting that the BCR gene segments may influence the kinase activity of the fusion gene product, and hence determine the specificity for transformation of committed lymphoid or pluripotent hematopoietic progenitors.77

Patients with Ph+ ALL have a dismal prognosis, even in contemporary programs of multiagent chemotherapy,6,20,25,56 and are candidates for experimental therapy early in the course of their disease. Preliminary data suggest that adolescents and young adults with Ph+ ALL may have a more favorable outcome with bone marrow transplantation,56,76 an approach now being investigated for children with Ph+ ALL in first remission. A recent study suggests that children with Ph+ ALL and monosomy 7 may have an even shorter survival period than observed for patients with the Ph chromosome only.79 The only reported long-term survivors of Ph+ child- hood ALL or Ph+ CML.* Thus, it is likely that cases with chromosomal translocations do not have an adverse prognosis. The t(1;19)(q23:p13) in B-cell precursor ALL. In 1983, Carroll et al56 reported that some cases of pre-B ALL (positive for cytoplasmic Ig but negative for surface Ig) had leukemic cells with a specific chromosomal translocation,

### Table 3. Nonrandom Chromosomal Translocations in Childhood ALL

<table>
<thead>
<tr>
<th>Nonrandom Translocation</th>
<th>Involved Genes</th>
<th>Predicted Protein Product</th>
<th>Frequency (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-B/early pre-B cells</td>
<td>t(9;22)(q34;q11)</td>
<td>ABL BCR P185br-abl</td>
<td>3-5</td>
<td>6, 55-58, 61, 62, 69-75, 77-80</td>
</tr>
<tr>
<td>t(1;19)(q23;p13)</td>
<td>PRL EZA EZA-PRL fusion protein</td>
<td>5-6</td>
<td>53, 81-82</td>
<td></td>
</tr>
<tr>
<td>t(11;q23;v)</td>
<td>Unknown Unknown</td>
<td>3</td>
<td>183-186</td>
<td></td>
</tr>
<tr>
<td>t(4;11)(q21;q23)</td>
<td>Unknown Unknown</td>
<td>2</td>
<td>2, 27, 167-182, 188</td>
<td></td>
</tr>
<tr>
<td>t(1;11)(p32;q23)</td>
<td>Unknown Unknown</td>
<td>&lt;1</td>
<td>183, 185</td>
<td></td>
</tr>
<tr>
<td>t(10;11)(p14-p15;q22)</td>
<td>Unknown Unknown</td>
<td>&lt;1</td>
<td>183, 185</td>
<td></td>
</tr>
<tr>
<td>t(11;19)(q23;p13)</td>
<td>Unknown Unknown</td>
<td>&lt;1</td>
<td>183-186</td>
<td></td>
</tr>
<tr>
<td>t9;11(p21-22;q23)</td>
<td>Unknown Unknown</td>
<td>&lt;1</td>
<td>27, 183, 185</td>
<td></td>
</tr>
<tr>
<td>t12;v(p12-p13;v)</td>
<td>Unknown Unknown</td>
<td>5</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>dic9;12(p11-p12;p12)</td>
<td>Unknown Unknown</td>
<td>1-2</td>
<td>31, 199</td>
<td></td>
</tr>
<tr>
<td>dic7;9(p13;p11)</td>
<td>Unknown Unknown</td>
<td>&lt;1</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

T cells

<table>
<thead>
<tr>
<th>Nonrandom Translocation</th>
<th>Involved Genes</th>
<th>Predicted Protein Product</th>
<th>Frequency (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14)(p13;q11)</td>
<td>Unknown TCRα/TCRβ</td>
<td>1</td>
<td>17, 82, 132-139</td>
<td></td>
</tr>
<tr>
<td>t(11;14)(p15;q11)</td>
<td>TGG1 TCRα/TCRβ Zinc-finger protein (rhombotin)</td>
<td>Rare</td>
<td>124, 125, 141-144</td>
<td></td>
</tr>
<tr>
<td>t(10;14)(q24;q11)</td>
<td>Unknown TCRα/TCRβ</td>
<td>&lt;1</td>
<td>126, 130, 153, 154</td>
<td></td>
</tr>
<tr>
<td>inv(14)(q11q32.3)</td>
<td>TCRα/TCRβ Unknown</td>
<td>&lt;1</td>
<td>17, 126, 146-149</td>
<td></td>
</tr>
<tr>
<td>t(1;14)(p23-q34;q11)</td>
<td>TAL1 TCRα/TCRβ Helix-loop-helix protein</td>
<td>Rare</td>
<td>131, 156-158</td>
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<tr>
<td>t8;14(q24;q11)</td>
<td>MYC TCRα/TCRβ Helix-loop-helix protein</td>
<td>Rare</td>
<td>17, 82, 121, 127-129, 150-152</td>
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<tr>
<td>t7;v(1q35;v)</td>
<td>TCRβ Unknown</td>
<td>2</td>
<td>17, 166-162</td>
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<tr>
<td>t7;9(q34-q36;v34)</td>
<td>TCRβ Unknown</td>
<td>Rare</td>
<td>161, 163, 164</td>
<td></td>
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<tr>
<td>t7;9(q34-q36;v32)</td>
<td>TCRβ Unknown</td>
<td>Rare</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>t7;19(q35;13)</td>
<td>TCRβ LYL1 Helix-loop-helix protein</td>
<td>Rare</td>
<td>161, 166</td>
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B cells

<table>
<thead>
<tr>
<th>Nonrandom Translocation</th>
<th>Involved Genes</th>
<th>Predicted Protein Product</th>
<th>Frequency (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>t8;14(q24;q32.3)</td>
<td>MYC IGH Helix-loop-helix protein</td>
<td>2</td>
<td>96-100, 106</td>
<td></td>
</tr>
<tr>
<td>t8;22(q24;q11)</td>
<td>MYC IGL Helix-loop-helix protein</td>
<td>0.3</td>
<td>96, 98, 104, 105</td>
<td></td>
</tr>
<tr>
<td>t2;8(p11-p12;q24)</td>
<td>IGK MYC Helix-loop-helix protein</td>
<td>Rare</td>
<td>97, 98, 101-103</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ABL, cellular homologue of the Abelson murine leukemia virus oncogene; BCR, gene containing the breakpoint cluster region involved in Ph translocation; PRL, pre-B-cell leukemia gene; E2A, gene for Ig enhancer binding proteins E12/E47; TCR, T-cell receptor gene; TGG, T-cell translocation gene; IGH, Ig heavy-chain gene; TAL, T-cell acute leukemia gene; MYC, cellular homologue of the transforming sequence of the avian myelocytomatosis virus; IGK, Ig l light-chain gene; IGL, Ig l light-chain gene; LYL, lymphoid leukemia gene.
t(1;19)(q23;p13). Subsequent studies have identified this translocation in approximately 25% of cases of pre-B-cell ALL; however, the t(1;19) was also found in approximately 1% of childhood pre-B ALL cases. Overall, the t(1;19) is found in approximately 5% to 6% of childhood ALL cases, making it the most common chromosomal translocation. Among pre-B cases, those with the t(1;19) were significantly more likely to have a pseudodiploid karyotype than those with other translocations or no translocations. Hyperdiploidy >50 was notably absent in the cases with a t(1;19). In our earlier study, we suggested that the increased frequency of chromosomal translocations in leukemic cells was largely responsible for the adverse outcome reported for children with pre-B ALL, although at that time it was not possible to implicate any single alteration as the major causative factor. By studying a larger number of patients, we found that the high-risk features formerly ascribed to pre-B-cell ALL are closely associated with the t(1;19): increased leukocyte count and a high frequency of black patients. Our most recent results, based on a limited patient sample and relatively short follow-up, suggest that more effective treatment can offset the negative prognostic impact of this translocation, illustrating once more the overriding importance of therapy in determining outcome.

The critical chromosomal rearrangement in the t(1;19) appears to be the der(19) marker with fusion of the long arm of chromosome 1 to the short arm of chromosome 19, because the translocation is frequently unbalanced with loss of the der(1) marker chromosome. Mellentin et al. have mapped the E2A gene, which codes for the Ig enhancer binding factors E12 and E47, to chromosome region 19p13.2-p13.3. In their study, each of 10 pre-B-cell leukemias or cell lines carrying the t(1;19) contained rearrangements of the E2A gene. These rearrangements altered the E2A transcriptional unit, resulting in synthesis of a fusion transcript containing 5' sequences of the E2A message and 3' sequences from the gene on chromosome 1.

Recently, the fusion cDNAs were cloned and shown to code for an 85- to 90-Kd protein comprising two thirds of the amino-terminal elements of E2A fused to a chromosome 1-derived protein. The chimeric protein lacks the DNA binding and dimerization motifs of the E2A protein; these motifs are replaced by the putative DNA binding domain of a homeoprotein from chromosome 1. The homeobox-containing gene at 1q23 was named PRL (pre-B-cell leukemia). It was postulated that the E2A-PRL fusion gene is an oncogene and that the chimeric protein contributes to development of ALL by altering expression of genes normally responsive to the Prl homeoprotein. For cases with the translocation, molecular diagnosis and identification of minimal residual disease are now possible, using the polymerase chain reaction to detect the t(1;19)-specific fusion transcript.

Translocations in B-cell leukemia-lymphoma. B-cell leukemia, found in 1% to 3% of cases of childhood ALL, is usually characterized by FAB L3 cellular morphology, the presence of monoclonal Ig on the surface of malignant cells, and extramedullary diseases (eg, lymphomatous masses, CNS disease). B-cell ALL invariably contains one of three specific chromosomal translocations: the t(8;14)(q24; q32.3) or, less commonly, either the t(2;8)(p11-p12;q24) or the t(8;22)(q24;q11). In some cases, there may be additional karyotypic abnormalities such as dup(Iq), t(1;19)(q23; p13), or the Ph chromosome.

Molecular investigations of the translocations involved in B-cell neoplasias have yielded valuable insight into the pathogenesis of these diseases. In cases with the t(8;14), the MYC proto-oncogene is translocated from its normal position on chromosome 8 into the heavy-chain gene on chromosome 14 adjacent to the coding sequences of the Ig-constant region. The coding sequences of the Ig-variable region generally are reciprocally translocated to the distal tip of chromosome 8. In the variant translocations, the MYC gene remains on chromosome 8 and either the K or the L light-chain genes located on chromosomes 2 and 22, respectively, are translocated to a chromosome region distal to the MYC gene. Thus, as a result of translocation, one allele of the MYC proto-oncogene is relocated in proximity to an Ig gene. The recombination between the MYC gene and the Ig gene appears in some instances to represent a misrecognition of the MYC gene sequences by a recombinase involved in Ig gene rearrangement.

The MYC proto-oncogene product acts in the nucleus and appears to be involved in the regulation of the transition of cells from a resting to a proliferative state. The translocations in B-cell ALL are thought to dysregulate MYC expression through an array of molecular changes that lead to malignant transformation or proliferation, including removal of the promoter sequences from the coding region of the MYC gene, repositioning of Ig gene enhancers close to the MYC gene, or mutations of the MYC gene. Indeed, in transgenic mice, the MYC oncogene driven by Ig enhancers frequently induces malignant B-cell lymphoma. An activated MYC gene also causes tumorigenic conversion when it is introduced into human Epstein-Barr virus-infected lymphoblastoid cells.

A large malignant cell burden and CNS involvement adversely influence the treatment outcome of patients with B-cell neoplasias. For example, B-cell non-Hodgkin lymphomas share the cytogenetic and molecular genetic features of B-cell ALL but respond much better to similar therapy. Even in B-cell ALL, several contemporary multiagent chemotherapy programs yield an estimated 50% long-term event-free survival.

Translocations involving the T-cell receptor loci. The demonstration that specific translocations involve the Ig gene loci in B-cell malignancies suggested that the T-cell receptor (TCR) genes might serve as sites for chromosomal rearrangements in T-cell ALL. This hypothesis has proved to be correct and altered expression of proto-oncogenes flanking breakpoints of chromosomes involved in specific rearrangements with Ig or TCR genes has been a consistent finding in B- and T-cell translocations. The β- and γ-genes of the TCR (TCRB and TCRγ) have been mapped to the chromosomal regions 7q32-q36 and 7p15, respectively, while α- and δ-genes (TCRA and TCRδ) have been found to be physically adjacent and interspersed on chromosome 14q11-1q3. Several nonrandom chromosomal rearrangements involving
the TCRα/TCRδ gene region have been found in T-cell neoplasms, including t(11;14)(p13;q11), t(11;14)(p15;q11), t(1;14)(p32-p34;q11), t(1;14)(p13;q11), t(10;14)(q24;q11), and t(1;14)(p32-p34;q11) (Table 3).

The t(11;14)(p13;q11) occurs in about 10% of childhood T-cell ALL cases. Molecular analysis has shown that the translocation involves the TCRα/TCRδ locus on chromosome 14q32.3, and a region termed T-ALL locus (or a putative oncogene, TCL2) on chromosome 11. Although a transcribed gene has not yet been identified within the T-ALL region, the breakpoints consistently fall within a region of less than 25 kb, suggesting that this rearrangement plays a role in the development of T-cell ALL in these cases. The commonly deleted region in Wilms' tumor is located at the 11p13 region, but the translocation breakpoint on chromosome 11 of T-cell ALL does not appear to map to the same locus. A second translocation involving chromosomes 11 and 14, t(11;14)(p15;q11), is less common with only a few cases reported to date. This translocation involves the TCRα/TCRδ locus on chromosome 14q32.3, and TGG1 (T-cell translocation gene 1, which encodes a potential zinc-finger DNA-binding protein) on chromosome 11. Although TGG1 is expressed developmentally and segmentally in the murine CNS, extensive studies have failed to show its expression in normal T cells. Thus, a gene that appears to be involved in normal CNS development is rendered transcriptionally active by chromosomal translocation in T cells, where its aberrant expression in all likelihood contributes to leukemogenesis.

Although inv(14)(q11q32.3) chromosomes associated with childhood ALL have not yet been characterized at the molecular level, they appear indistinguishable from the same abnormality in adult T-cell malignancies (eg, lymphoblastic lymphoma and chronic lymphocytic leukemia, which have been extensively studied). In a single case, chromosome 14 inversion generated a hybrid gene consisting of an Ig-variable region gene fused to the joining and constant region segments of the TCRα gene. More commonly, however, the 14q32 breakpoints of inv(14)(q11q32.3) chromosomes occur outside the Ig heavy-chain locus, and thus are likely to involve a distinct genetic entity in 14q32.

In the t(8;14), the TCRα gene is rearranged to a position near the MYC proto-oncogene locus at 8q24, leading to transcriptional dysregulation of this gene. In one T-cell leukemia with the t(8;14), aberrant joining of chromosome 8 sequences to a Jα segment has been demonstrated, suggesting that, similar to the mechanism postulated for B-cell malignancies, mutations in physiologic V-D-J joining can mediate chromosomal rearrangement in T cells. In T-cell ALL with the t(10;14)(q24;q11), the breakpoint at 14q11 involves the TCRα/TCRδ locus, and the translocation juxtaposes the TCR gene to a conserved and activated locus, a putative proto-oncogene TCL3 at 10q24.

In a study of a stem-cell line with the t(1;14), two groups of investigators suggested that the translocation occurred during an attempt at Δ4-Δ6, joining and showed that sequences (termed TCL5 or SCL) at band p32 of chromosome 1 are transcribed as a result of rearrangement. Recently, Chen et al analyzed two cases of T-cell ALL with the t(1;14). They found that chromosome 14 breakpoints occur within the TCRα/TCRδ locus and that the chromosome 1 breakpoints lie just 1 kb apart, suggesting that this region harbors a genetic locus (designated as TAL1 for T-cell acute leukemia) involved in leukemogenesis. Moreover, they have identified sequences within the locus that potentially encode a helix-loop-helix motif, which is found in a number of transcriptional-activator proteins involved in the control of cell growth and differentiation.

The 4q23-q36 region containing the TCRβ gene was also found to be involved in T-cell ALL. Structural rearrangements affecting 7qter are subtle and could go undetected, which would explain in part the relative scarcity of reports of such cases. Indeed, with improved techniques, 4q32-4q36 rearrangements have been identified as frequently as the 14q11-q13 rearrangements in childhood T-cell ALL.

A unique case of T-cell ALL was reported to have a pericentric inversion of chromosome 7 (p15q34) with breakpoints in the proximity of chromosomal bands containing the loci of the TCRβ and TCRγ genes. Molecular analysis of DNA from T-cell cases with a t(7;9)(q34-q36;q34) showed that the TCRβ gene is recombined with DNA from chromosome 9. Recently, Mellenti et al found that a t(7;19)(q35; p13) results in truncation of the LYL1 gene and its head-to-head juxtaposition with the TCR8 gene. The predicted protein product of the LYL1 gene is similar to the TAL1 protein in that it contains a potential helix-loop-helix DNA-binding motif, indicating a probable role for genes of this family in the malignant transformation of lymphocytes.

Unlike cases of B-cell ALL, which almost invariably have specific translocations involving an Ig gene locus, the overall frequency of translocations in T-cell ALL is about 44%, and half of these cases have the breakpoints in regions to which the TCR genes have been mapped. It should be noted that chromosomal alterations involving regions of TCR gene loci may also occur in occasional cases of B-cell precursor ALL. Moreover, there is no apparent relationship between particular translocations and the stage of thymocyte differentiation of leukemic blasts. In addition, while leukemic cell chromosomal abnormalities in general have been found to correlate with a poor outcome in T-cell ALL, insufficient cases have been studied to determine the unique prognostic impact of specific rearrangements.

Rearrangements of 11q23. Acute leukemia with the t(4;11)(q21;q23) has been associated with hyperleukocytosis, splenomegaly, age less than 1 year at presentation, and a poor prognosis. Ultrastructural, immunophenotypic, and in vitro culture studies have demonstrated marked lineage heterogeneity in cases with this translocation. While most cases have been classified as early B-lineage ALL (CD19+, HLA-DR+, CD10+), others have had myelomonocytic characteristics, mixed-lineage features, undifferentiated phenotype, or rarely T-cell or B-cell features. Leukemic cells with this translocation can be induced to express monocytic features in vitro. Other translocations with breakpoints involving band q23 of chromosome 11, including the t(9;11)(p21;q23) and the t(11;19)(q23;p13), have also been associated with
lymphoid, myeloid, or mixed-lineage expression.\textsuperscript{27,183-185} Taken together, these findings suggest that leukemias with an 11q23 rearrangement arise from multipotential progenitor cells capable of differentiation in both the lymphoid and myeloid lineages.\textsuperscript{27,186} One study suggests that the heterogeneity in the breakpoints of chromosome 11 influences the differentiation of leukemic stem cells with the t(11;19).\textsuperscript{187}

Raimondi et al\textsuperscript{183} recently analyzed the clinical characteristics of children with ALL and the 11q23 abnormality. Overall, 5.7% of childhood ALL cases were found to have this abnormality. Children with the 11q23 translocations had significantly higher leukocyte counts, and were more likely to be black and younger by comparison to patients with other abnormalities. The impact of specific translocations on clinical outcome could not be assessed because of the relatively small sample size. In this regard, Heerema et al\textsuperscript{188} have suggested that the t(4;11), and not a breakpoint at 11q23, was the factor associated with poorer prognosis in their patients. However, the independent prognostic significance of the t(4;11) is still uncertain because of its strong correlation with other adverse presenting features such as hyperleukocytosis and age less than 1 year.

\textbf{9p Abnormalities.} Deletions or unbalanced translocations of the short arm of chromosome 9, including bands 9p21 and 22, have been reported in 7% to 14% of patients with ALL.\textsuperscript{7,189-191} Kowalczyk and Sandberg\textsuperscript{189} first reported seven patients with ALL and partial deletion of the short arm or monosomy of chromosome 9. They suggested that this is a nonrandom karyotypic abnormality, which occurs in association with acute leukemia of the T-cell phenotype, a high leukemic cell burden, and a poor prognosis. Chilcote et al\textsuperscript{190} subsequently reported an analysis of eight children or adolescents with ALL and 9p abnormalities, suggesting that the chromosomal changes were associated with "lymphomatous" ALL, which often has a T-cell phenotype. Supporting earlier observations, Smith et al\textsuperscript{191} reported abnormalities of chromosome 9 in leukemic cells from three of six children with T-cell ALL but in none of 20 with B-cell precursor ALL.

Recent studies of large numbers of patients have shown a broader spectrum of involvement.\textsuperscript{192} Carroll et al\textsuperscript{193} found 9p abnormalities in the leukemic cells of 7 of 100 children. Only one of these cases had lymphomatous features and all had early B-lineage ALL. We found 9p abnormalities in 40 (10%) of 398 consecutive childhood ALL cases.\textsuperscript{192} Compared with cases lacking 9p abnormalities, these 40 children were significantly older, had higher leukocyte counts, more "lymphomatous" disease features (T-cell phenotype in 26%), and an increased rate of extramedullary relapse.\textsuperscript{192} However, the finding of an abnormal chromosome 9p was not specific for lymphomatous ALL or T-cell lineage, as most cases did not have these features.

A cluster of interferon-\(\alpha\) genes and the interferon-\(\beta\)1 gene have been localized to the 9p22 region.\textsuperscript{193} Diaz et al\textsuperscript{194} found homozygous or hemizygous deletion of the interferon gene cluster in 7 of 15 cell lines derived from patients with ALL. While the gene deletions were associated with visible cytogenetic deletions or other 9p rearrangements in four cases, the deletions were submicroscopic in three. Recently, these investigators examined 62 cases of ALL and found deletions of the interferon genes in 18 (28%).\textsuperscript{195} Four cases had homozygous deletions of the interferon-\(\alpha\) gene cluster; one of these also had a homozygous deletion and three had hemizygous deletions of the interferon-\(\beta\)1 gene. The other 14 patients had hemizygous deletions of both the interferon-\(\alpha\) gene cluster and the interferon-\(\beta\)1 gene. Interestingly, 8 of the 18 cases had submicroscopic deletions. The investigators speculated that the loss of one or more of the interferon genes may be related to malignant proliferation of ALL, because the interferons are known to affect cell proliferation and differentiation.\textsuperscript{196} Alternatively, the loss of a closely linked tumor-suppressor gene may be the relevant genetic defect associated with leukemogenesis in cells with these deletions.

\textbf{Abnormalities of 12p and 6q.} Rearrangements involving 12p12 and deletion of the long arm of chromosome 6 (6q-?) are frequent nonrandom abnormalities in childhood ALL, occurring in 10\%\textsuperscript{197} and 11\%\textsuperscript{189,198} of all cases, respectively. Among the 23 cases with 12p12 abnormalities reported by Raimondi et al,\textsuperscript{197} 18 had "common," 3 pre-B, and 2 T-cell ALL, a distribution not substantially different from those of childhood ALL in general. However, none of the cases had prognostically favorable hyperleukocytosis >50 and their median leukocyte count (30 \(\times\) 10\(^9\)/L) was higher than cases lacking this abnormality. Two nonrandom translocations, t(7;12)(q11; p12)\textsuperscript{199} and dic(9;12)(p11-p12;p12),\textsuperscript{31,199} have breakpoints in this region. Of the eight reported cases with the dic(9;12), seven had hypodiploid karyotypes, seven were boys, and all remained in remission.\textsuperscript{187} The prognostic significance of the 12p12 abnormality is not yet known. It may be of interest that the human cellular homolog of the k-ras-2 gene was mapped in the region of the 12p12 breakpoint.\textsuperscript{200,201}

The clinical features and outcome of childhood cases with 6q- did not differ appreciably from those lacking this abnormality.\textsuperscript{198} All 45 cases reported by Hayashi et al\textsuperscript{199} had deletion of the 6q21 band, suggesting that this might be the locus of a recessive tumor-suppressor gene whose absence contributes to malignant transformation or proliferation.

\textbf{Chromosomal abnormalities in mixed-lineage leukemia.} Acute leukemia with blast cells expressing both lymphoid and myeloid features, so-called acute mixed-lineage leukemia or biphenotypic leukemia, is a well-recognized clinical entity.\textsuperscript{202-207} In our recent report of 372 children with ALL, 61 cases (16.4%) were found to have blast cells expressing myeloid-associated antigens.\textsuperscript{207} Despite their relatively frequent occurrence, the pattern of karyotypic abnormalities in this group has not yet been defined. In the limited cytogenetic studies of acute mixed-lineage leukemia, only t(9;22)\textsuperscript{17,204,208,209} and 11q23 translocations\textsuperscript{18,172,175,180,210} have been consistently associated with this phenotype. Recently, 14q32 translocations other than the t(8;14)(q24;q32) were also correlated with the mixed-lineage phenotype.\textsuperscript{211}

\textbf{Apparently unique chromosomal translocations.} In our earlier study of 161 children with newly diagnosed ALL, 28\% of the cases were found to have chromosomal translocations, of which 42\% were judged to be "random," in that they have only been identified in single cases.\textsuperscript{4} The presence of any translocation, random or otherwise, was associated with a sixfold-greater risk of early failure, and was the single strongest predictor of treatment outcome. However, several
contemporary intensive treatment regimens appear to have nullified the adverse prognostic effect of random translocations. With further study, it is likely that many of the so-called random translocations will be identified in additional cases and thus may pinpoint important new gene rearrangements. Whether every translocation alters a specific gene or genes in ways that promote leukemogenesis remains to be determined.

MULTIPLE LEUKEMIC CELL LINES

Clonal evolution of cytogenetic abnormalities, in which a leukemic cell population contains two or more sublines with related chromosomal abnormalities, is a relatively common finding in ALL. Almost one fourth of the ALL cases have shown evidence of this process. The clinical significance of this karyotypic finding remains uncertain. In approximately 1% of newly diagnosed cases of ALL, "cytogenetically independent" cell populations can be found. To investigate the clonality of these unusual leukemias, we examined the neoplastic cells for inactivation of X-linked genes by methylation, which occurs at random early in embryogenesis. Leukemic cells from each of the three patients heterozygous for an X-linked restriction-fragment-length polymorphism showed inactivation of a single allele, suggesting that both apparently independent cell populations developed from a common progenitor. Thus, in these cases the karyotypic abnormalities may be a late event in the multistep process of malignant transformation. However, because there is a 50% chance that two independent clones expressed the same allele, there remains a one in eight probability that the three cases are truly biclonal. Additional leukemias with more than one cytogenetically distinct line need to be studied to definitively address this issue.

CYTOGENETIC FINDINGS AT RELAPSE

Clonal evolution of cytogenetic findings from diagnosis to relapse occurs frequently in ALL. In most instances, the karyotypes at diagnosis are related to those at relapse. In a study by the Third International Workshop on Chromosomes in Leukemia, clonal evolution appeared more often in patients who had an abnormal clone at diagnosis, had been treated intensively, and had a long initial remission duration. Moreover, the median survival time following relapse was longer for patients in whom no abnormal clone was found either at diagnosis or at relapse. In the study by Williams et al of 51 children with ALL at diagnosis and at relapse, clonal evolution was noted in 79% of the cases whose cells generally acquired one or more new structural abnormalities.

We found an entirely different karyotype at relapse in six of eight cases with loss of expression of the common ALL antigen or conversion to acute myeloid leukemia at relapse. In our subsequent study of secondary acute myeloid leukemia in children treated for ALL, sequential cytogenetic studies showed entirely different karyotypes in 9 of 10 patients. Although the cytogenetic findings suggest induction of a second neoplasm in these patients, the independent clonal nature of these myeloid leukemias needs to be confirmed by studies with X-chromosome-inactivation markers in heterozygous female patients. Univariate analysis showed that T-cell immunophenotype at diagnosis of ALL and treatment with an epipodophyllotoxin (either teniposide or etoposide, or both) or irradiation were significantly associated with the development of acute myeloid leukemia. However, determination of the relative importance of these treatment components in the pathogenesis of this complication was confounded by the fact that all patients with T-cell leukemia received epipodophyllotoxins and radiation therapy. It is remarkable that over half of the cases of secondary acute myeloid leukemia in this study had a chromosomal abnormality affecting the 11q23 region, which has been associated with malignant transformation in lymphoid, myeloid, and mixed-lineage leukemia at diagnosis. More recently, Prieto et al reported that each of their three cases with secondary AML after prednisone, vincristine, 6-mercaptopurine, methotrexate, teniposide, and cytarabine treatment for ALL had 11q23 abnormalities, confirming our observation. Interestingly, we have encountered two other children who developed acute myeloid leukemia with blast cells exhibiting 11q23 abnormalities after treatment for non-Hodgkin lymphoma and neuroblastoma, respectively; both patients had received treatment regimens including teniposide. Further studies of leukemic cells at relapse should provide a better understanding of the nature of the development of drug resistance and the possible induction of new leukemic clones by potentially carcinogenic treatment.

SUMMARY

Virtual all cases of childhood ALL have chromosomal abnormalities and half contain translocations, which are nearly equally divided between random and nonrandom rearrangements. Nonrandom chromosomal abnormalities have been correlated with leukemic cell lineage, the degree of cell differentiation, and the specific gene involved at the molecular level. Many cytogenetic findings have prognostic
significance; however, the adverse influence of certain changes, including most chromosomal translocations, may in fact be offset by the greater cytoreductive effects of intensified therapy. Table 4 summarizes the relation of selected karyotypic findings to treatment outcome in patients treated on contemporary protocols. Among all of the chromosomal abnormalities identified in childhood ALL, hyperdiploidy >50 has been associated with the most favorable prognosis. At the opposite end of the spectrum, the treatment outcome for patients with classical Ph\(^+\) or hypodiploid ALL is very poor even in programs of intensive chemotherapy; alternative treatment such as bone marrow transplantation should be considered for such patients. Cases with the t(4;11)(q21;q23) also have a very poor clinical outcome, but the adverse prognosis may be limited to the infant or adolescent age groups.\(^{18}\) The prognostic significance of other nonrandom translocations, such as t(1;19)(q23;p13) and several other abnormalities, needs to be further assessed in larger numbers of patients. Finally, as more is learned about the molecular pathology underlying these rearrangements, it may be possible to develop new therapeutic agents that are specifically targeted to interfere with the aberrant gene products expressed by human leukemic cells.

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Biology and clinical significance of cytogenetic abnormalities in childhood acute lymphoblastic leukemia

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