Clinical and Biologic Features of Childhood T-Cell Leukemia With the t(11;14)

By Raul C. Ribeiro, Susana C. Raimondi, Frederick G. Behm, John Cherrie, William M. Crist, and Ching-Hon Pui

Cytogenetic analysis of cells from 622 consecutive patients with newly diagnosed acute lymphoblastic leukemia (ALL) and successful G-banding chromosome studies disclosed seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a T-cell immunophenotype. The t(11;14)(p13;q11) occurred in six cases with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11). Leukemia cells in all eight cases had a seven cases with the t(11;14)(p13;q11) and one with the t(11;14)(p15;q11).

CONSISTENT KARYOTYPIC abnormalities have provided clues to the mechanism(s) of malignant transformation and disease progression.1 Molecular studies of T-cell leukemias and lymphomas have disclosed several chromosomal translocations involving genes that code for the polypeptide chains of the T-cell receptor (TCR). Among the nonrandom translocations in childhood T-cell acute lymphoblastic leukemia (ALL), the t(11;14)(p13;q11) is the most common.3,4 This translocation involves TCR alpha/delta (TCR A/D) genes on chromosome 14 (14q11) and a region on chromosome band 11p13 termed the T-ALL bcr locus (with a putative oncogene, TCL2).5-11 Another translocation involves the same region on chromosome 14 but a different region on chromosome 11 (11p15), which may carry a stage-specific differentiation gene (TTG1, rhombo tin).1213 Despite abundant information regarding the molecular aspects of these two translocations, there has been virtually no information about the clinical and biologic characteristics of patients in whom they are present. We describe the clinical and laboratory features of T-cell ALL with the t(11;14)(p13;q11) in seven children and the t(11;14)(p15;q11) in another child.

PATIENTS AND METHODS

Patients. From December 1979 to April 1990, 875 consecutive children with newly diagnosed ALL were admitted to St. Jude Children’s Research Hospital. Of those, successful G-banding chromosome studies were performed for 622 cases. The diagnosis of ALL was based on morphologic criteria of the French-American-British (FAB) classification system14 and negative myeloperoxidase staining. Of the 141 cases known to have the T-cell ALL immunophenotype, adequate bone marrow samples were available for G-banding chromosome studies in 103. Among the 103 T-cell ALL cases, there were seven (6.8%) with the t(11;14)(p13;q11) (Fig 1A) and one (1%) with the t(11;14)(p15;q11) (Fig 1B). These translocations were not present in any cases of non-T-cell ALL. All of the patients were treated according to one of total therapy studies XII,1516. Informed consent was obtained for all patients, and the investigation was approved by the institution’s clinical trials review committee. The karyotypes of five of the eight patients have been reported previously.17 Six additional patients with the t(11;14)(p13; q11) and three with the t(11;14)(p15;q11) about whom adequate information was available were identified in the literature.1821

Cytogenetic studies. Bone marrow samples taken at diagnosis were processed according to the direct method of Williams et al.22 Chromosomes were identified and classified according to the International System for Human Cytogenetic Nomenclature.23

Blast cell phenotyping. Leukemic blast cells from bone marrow aspirates were separated on a Ficoll-Hypaque gradient. Cell-surface antigens were detected by a standard indirect immunofluorescence assay using a panel of monoclonal antibodies (MoAbs) including HLD-DR, CD1(T6), CD2(T11), CD3(T3), CD4(T4), CD5(T1 or T101), CD7(Leu7), CD8(T8), CD10(CALLA), CD19(B4), CD20(B1), CD13(My7), CD15(My1), and CD33(My9). Cells were analyzed for fluorescence activity by flow cytometry (Coulter EPICS C, Hialeah, FL) or fluorescence microscopy. Results were considered positive if greater than 20% of the cells expressed a particular antigen. Blast cells were also tested for surface and cytoplasmic Ig and rosette formation with sheep erythrocytes. A case was considered to be of T-cell origin if the blast cells formed rosettes with sheep erythrocytes or expressed at least two of the CD7, CD5, and CD7 antigens. T-cell cases were further subclassified according to a modification of the scheme of intrathymic ontogeny proposed by Reinherz et al:23 stage I (early) = CD7+, CD2+, CD4, CD5, CD1-, CD3-, CD8+, stage II (intermediate) = CD7+, CD2+, CD3+, CD5+, CD1-, CD3+, CD4+, and stage III (late) = CD7+, CD2+, CD3+, CD5+, CD1+, CD3+ and either CD4+ or CD8+. Molecular genetic analysis. Purification of genomic DNA extracted from marrow blast cells obtained at the time of diagnosis, restriction enzyme digestion, gel electrophoresis, and Southern blotting were performed as previously described.24 The DNA probes and hybridization conditions used to detect the genes
T-CELL LYMPHOID LEUKEMIA TRANSLOCATIONS

Fig 1. Partial G-banded karyotypes demonstrating the t(11;14)(p13;q11) (A) and the t(11;14)(p15;q11) (B). Arrows indicate the sites of breakpoints.

...coding for the human \( \beta \) and \( \gamma \) chains of the TCR receptor or the heavy chain of the Ig molecule were also reported previously.\(^2\)

**Statistical analysis.** Differences in clinical and laboratory features among cytogenetic subgroups were analyzed by using Fisher's exact test. For variables measured on a continuous scale, differences in the distribution of clinical features were evaluated by using the Wilcoxon rank sum test.

**RESULTS**

Presenting clinical and laboratory features of our seven patients with T-cell ALL and the t(11;14)(p13;q11) are summarized in Table 1. There were five boys and two girls whose ages ranged from 2 to 16 years (median, 5 years). These cases were characterized by high leukocyte counts (median, \( 157 \times 10^9/L \)); high hemoglobin levels (median, 10.8 g/dL); and markedly elevated serum lactic dehydrogenase (LDH) levels (median, 3248 IU/L). Central nervous system (CNS) leukemia was present in two patients and mediastinal mass in six. Lymphoblast morphology was FAB L1 in six cases and L2 in one case.

The immunophenotypes of leukemic cells from the seven patients with the t(11;14)(p13;q11) are shown in Table 2. Cells from two patients were studied before MoAbs were available. Cell samples from all seven patients expressed sheep erythrocyte receptors and/or CD2 (T11) surface antigen. Of five cases tested, all simultaneously coexpressed CD4 and CD8 and three expressed CD3. None of the cells analyzed expressed surface Ig (seven cases), intracytoplasmic Ig (seven cases), or myelomonocytic markers (three cases).

The 3.5-year-old boy with the t(11;14)(p15;q11) presented with an initial leukocyte count of \( 537 \times 10^9/L \). His leukemic cells had FAB L1 morphology and coexpressed CD4 and CD8 surface antigens. Of five cases tested, all simultaneously coexpressed CD4 and CD8 surface antigens (Table 3, case 14).

Leukemic cells from all eight patients with the t(11;14) had a modal chromosome number of 46 (Table 4). The t(11;14)(p13;q11) was the only translocation in five cases. Case 1 had an additional unrelated stem line with a del(6)(q24).

Analysis of DNA from six cases studied (3, 4, 5, 6, 7, and 14) disclosed no rearrangement of either Ig heavy chain or K light chain gene loci. All samples analyzed had rearrange-
Table 2. Immunophenotypes of Leukemia Cells From Patients With T-cell ALL and the t(11;14)(p13;q11)

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<th>Patient No.</th>
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<th>CD19</th>
<th>CD10</th>
<th>CD7</th>
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<th>CD2/E-R</th>
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<th>CD5</th>
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Published Cases (ref)

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Abbreviations: Neg, negative; Pos, positive; —, not assessed or not done.

Table 3. Clinical and Laboratory Features of Four Patients With T-cell ALL and the t(11;14)(p13;q11)

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<tr>
<th>Patient</th>
<th>Age(y)/Gender</th>
<th>Leukocyte count (x 10^9/L)</th>
<th>Hemoglobin (g/dL)</th>
<th>Platelet count (x 10^9/L)</th>
<th>Serum LDH levels (IU/L)</th>
<th>FAB classification</th>
<th>Mediastinal mass</th>
<th>CNS leukemia</th>
<th>CD7</th>
<th>CD1</th>
<th>CD2/E-R</th>
<th>CD3</th>
<th>CD5</th>
<th>CD4</th>
<th>CD8</th>
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<th>Survival (mo)</th>
<th>Type of failure</th>
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Abbreviations: Hem, hematologic relapse; —, not assessed or not done.

*Present study.
burden, did not differ significantly between T-cell ALL patients with these translocations would be expected to exert their influence on leukemia cell proliferation; hence, their involvement in the specific translocations were also found to be rearranged in some cases. Thus, studies of these cases provide important insight into molecular pathology underlying leukemogenesis.

Reinherz et al.24 have proposed a three-stage scheme of thymocyte differentiation and maturation based on sequential expression of surface antigens. Using this scheme, most T-cell malignancies can be classified as early, intermediate, or late stage of thymocyte differentiation.33,34 Our eight cases and five of seven described in the literature (Tables 2 and 3) expressed a profile of membrane surface antigens that has been associated with more mature thymocytes (CD4+, CD8+, and CD3+). Another interesting clinical aspect noted in six of the eight patients in this study and five of seven reported cases, was the presence of a mediastinal mass that was frequently present in patients with T-cell ALL having an intermediate-stage thymocyte phenotype.27

Six adverse events have occurred among our eight patients and six among the nine patients described in the literature. Two of our eight patients have developed AML, a rate that is not different than that in T-cell ALL cases in general.35 Whether or not patients with the t(11;14) fare less well than do others with T-cell ALL will require additional studies.

### ADDENDUM

Since this manuscript was submitted, we have encountered another T-cell ALL case with the t(11;14)(p13;q11) in a 14-year-old white male. Presenting features included a leukocyte count of 244 $\times 10^9$/L, a hemoglobin level of 13.7 g/L, a serum LDH of 4000 IU/L, and involvement of CNS, mediastinum, and testicles. The leukemic cell immunophenotype was that of intermediate-stage thymocyte differentiation (96% CD2+; 96% CD5+; 97% CD7+; 5% CD3+; 85% CD4+, and 94% CD8+). The child is in remission for 1+ month.

### ACKNOWLEDGMENT

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