Translocation 4;11 in Acute Lymphoblastic Leukemia: Clinical Characteristics and Prognostic Significance

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Banded bone marrow chromosome analyses have been done on 83 unselected patients with acute lymphoblastic leukemia (ALL). Seven patients, all with non-T, non-B ALL, had a translocation involving the long arms of chromosomes 4 and 11. Five of these patients, 4 children and 1 adult, were first studied at diagnosis, and the t(4;11) (q21;q23) was the only karyotypic abnormality. All 5 presented with a marked leukocytosis (>150 x 10^9/liter). Four of these 5 patients achieved a complete remission following the same intensive treatment regimen; however, remission duration and survival were very short (medians 2.5 and 8 mo, respectively). The fifth patient is currently receiving induction chemotherapy. The remaining 2 patients, both adults, were studied in relapse only, and had other karyotypic abnormalities in addition to the t(4;11). One of these relapse patients was a female whose clinical presentation and course were similar to those above. The last patient was a male who presented with a leukocyte count of 7 x 10^9/liter and maintained an initial complete remission for 37 mo. Our data suggest that patients who have a t(4;11) (q21;q23) at the time of diagnosis of ALL have a poor prognosis with conventional therapy and require a new therapeutic approach.

**BANDED BONE MARROW** chromosome studies have been done with considerable success in acute nonlymphocytic leukemia (ANLL). Distinct nonrandom karyotypic abnormalities have been identified and correlated with particular subtypes of ANLL and prognosis. Technical difficulties with short fuzzy chromatids and lack of clear bands have hampered such studies in acute lymphoblastic leukemia (ALL). Few nonrandom structural abnormalities have been identified in ALL and, with the exception of the Philadelphia chromosome, their relationship to prognosis is unknown. One structural rearrangement thus far found exclusively in patients with ALL is a translocation involving the long arms of chromosomes 4 and 11. A total of 8 patients with this anomaly have been reported. In this article we present 7 additional cases of the t(4;11) and describe the clinical characteristics and prognosis of this subgroup of ALL patients.

**MATERIALS AND METHODS**

**Cytogenetic Studies**

Bone marrow cells were obtained from heparinized posterior iliac crest aspirates, and the specimens were processed within 30 min of aspiration. Both direct preparations and 24-h cultures were done in cases 1-5; direct preparations only in cases 6 and 7. Cells in case 7 were studied in 1976 using a modification of the technique of Tjio and Whang. Cases 1-6 have all been studied since 1978 according to the method of Hozier and Lindquist.

Slides were first stained with 1:50 Geimsa:phosphate buffer solution and examined for suitable metaphases. Nonbanded analysis of modal chromosome number and karyotype were performed. Banded metaphase chromosomes were obtained in all cases using additional slides or by destaining the previous slides with a series of alcohols and restaining with the Wright’s technique of Sanchez. In all but case 1 at diagnosis, a minimum of 10 metaphases were examined, and the clonal abnormality confirmed in 7 or more cells. Additional slides or by destaining the previous slides with a series of alcohols and restaining with the Wright’s technique of Sanchez. In all but case 1 at diagnosis, a minimum of 10 metaphases were examined, and the clonal abnormality confirmed in 7 or more cells.

Photographs were taken on Kodak high contrast SO115 film using a Zeiss photomicroscope equipped with a green filter, and karyotypes were constructed from a single mitosis in the usual fashion.

**Patients**

A total of 83 unselected patients with ALL seen at the University of Minnesota Hospitals since October 1973 have had adequate mitoses for bone marrow chromosome analysis. One of 28 adults (ages 16–74 yr) and 4 of 38 children (ages 2 mo to 15 yr) first studied at diagnosis were found to have the t(4;11). This translocation was also seen in 2 of 14 adults and 0 of 3 children studied only in relapse.

All 7 patients with the t(4;11) presented acutely, without a history of prior hematologic disorder or serious illness. The diagnosis of ALL was made on the basis of morphology and cytochemical staining of the initial bone marrow aspirate and biopsy. Leukemic cells from all of the patients were tested as a minimum for receptors for unsensitized sheep erythrocytes (E) and surface immunoglobulin (Slg) using previously described methods for lymphocyte surface marker analysis.

Patients 1, 3, 4, and 5 were treated according to Childrens Cancer Study Group Protocol 163. Induction chemotherapy with vincristine, prednisone, and l-asparaginase was followed by central nervous system intensification with intrathecal methotrexate and cranial irradiation. Maintenance chemotherapy consisted of daily oral 6-mercaptopurine; weekly oral methotrexate; and pulses of vincristine, prednisone, cytarabine, cyclophosphamide, and Adriamycin. Patient 4 has just recently achieved remission. Patients 1 and 5 were unsuccessfully treated with further chemotherapy after first bone marrow relapse. Patient 3 underwent allogeneic marrow transplantation following achievement of a second remission, but relapsed again 6 mo later.
Induction of remission was difficult in patient 6, requiring 2 courses of cytarabine and adriamycin followed by 2 courses of vincristine, prednisone, cyclophosphamide and, in the fourth course, l-asparaginase. Central nervous system therapy as above was followed by maintenance chemotherapy with vincristine, prednisone, 6-mercaptopurine, and methotrexate. Marrow transplantation was performed at first relapse, but a sustained remission was not achieved.

Patient 7 was induced into remission with vincristine and prednisone, and maintained for 37 mo with 6-mercaptopurine, methotrexate, vincristine, prednisone, and cyclophosphamide. He survived only 4 mo after bone marrow relapse.

Patient 2 has just been diagnosed and begun on induction chemotherapy with vincristine, prednisone, and L-asparaginase. Because of the poor results in the previous 6 patients, he will receive a different, more intensive regimen of consolidation and maintenance chemotherapy.

Cytogenetic Studies

The results of the cytogenetic studies are summarized in Table 1. Patients 1–5 were first studied at diagnosis, and at that time the modal chromosome number was 46 and the t(4;11) (q21;q23) the sole karyotypic abnormality (Fig. 1). Remission marrow specimens were received from patients 3 and 5 only; both showed a reversion to a normal karyotype. Patient 1 developed a second chromosome abnormality at relapse, del(17)(p11), whereas patient 3 showed no evidence of clonal evolution through 2 relapses.

Patients 6 and 7 were studied only once, in relapse after therapy. Both showed abnormalities in addition to the t(4;11). The deleted number 4 chromosome in many of the cells of case 7 appeared less metacentric than that of the other patients. It is possible that the break point was closer to the centromere than q21, but banding was not clear enough to confirm this.

Patients

Partial clinical data are included in Table 1. Five of the patients were females and 2 were males, ranging in age from 8 wk to 31 yr (median 15 yr). All but case 7 presented with marked leukocytosis (7–574 × 10⁹/liter; median 283 × 10⁹/liter). All 7 patients had moderate anemia at diagnosis (Hb 6.4–9.3 g/dl; median 8.4 g/dl), but thrombocytopenia (<100 × 10⁹/liter) was present in only 4 patients. Splenomegaly was noted in all 7 patients, lymphadenopathy in

**Table 1. Clinical Characteristics at Diagnosis, Response to Therapy, and Cytogenetic Studies**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>WBC (x 10⁹/liter)</th>
<th>Duration of Initial Remission (mo)</th>
<th>Survival (mo)</th>
<th>Time of Study</th>
<th>Number of Cells Examined</th>
<th>Banded Karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Normal Clonal</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>8 wk</td>
<td>574</td>
<td>3</td>
<td>5</td>
<td>Diagnosis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>15 yr</td>
<td>572</td>
<td>–</td>
<td>½ +</td>
<td>Diagnosis</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>11 yr</td>
<td>449</td>
<td>2</td>
<td>16</td>
<td>Diagnosis</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>30 yr</td>
<td>283</td>
<td>2+</td>
<td>3+</td>
<td>Diagnosis</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>16 mo</td>
<td>151</td>
<td>8</td>
<td>11</td>
<td>Diagnosis</td>
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<td>0</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>31 yr</td>
<td>50</td>
<td>1</td>
<td>10</td>
<td>Relapse</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>17 yr</td>
<td>7</td>
<td>37</td>
<td>41</td>
<td>Relapse</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

**RESULTS**

**Fig. 1.** G-banded karyotype of case 4 at diagnosis showing the t(4;11)(q21;q23).
3, hepatomegaly in 2, and central nervous system involvement in only 1 (case 1) at diagnosis. None of the patients had a mediastinal mass. Lymphocyte surface marker analysis showed all 7 patients had non-T, non-B ALL.

Complete remission was achieved in all cases except patient 2, who has just recently begun induction; however, patient 7 was the only one who sustained this remission. Duration of initial remission in the other 5 cases ranged from 1 to 8 mo with a median of 2.5 mo. Patients 2 and 4 are the only survivors at present. The other patients died from their leukemia 5–41 mo after diagnosis (median survival 11 mo).

**DISCUSSION**

We have analyzed banded bone marrow chromosomes from 83 unselected patients with ALL and have identified 7 patients who had a translocation between the long arms of chromosomes 4 and 11. The first case in which banding allowed for positive identification of the t(4;11) in ALL was described by Oshimura et al. in 1977. Since that time 7 additional cases have been reported in the literature. To date, this translocation has not been found in other acute leukemias or lymphoproliferative disorders.

Including our 7 cases and the 8 from the literature, this translocation was found over a wide age range (4 days to 46 yr) in 8 children (<16 yr) and 7 adults (≥16 yr). The fact that 6 of the 8 children were ≤16 mo of age suggests that the t(4;11) may be an important finding in cases of congenital ALL; however, it is not restricted to such cases. Ten of these patients were females and 5 were males. All 7 of our patients and the 1 case from the literature on whom surface marker analysis was performed had non-T, non-B ALL.

Five of our cases and 7 from the literature were studied first at diagnosis. All 12 patients presented with marked leukocytosis (60–688 \times 10^9/liter; median 310 \times 10^9/liter). Moderate anemia and splenomegaly were constant features in our patients. The t(4;11) was the sole karyotypic abnormality seen in 11 of these cases. The 12th patient had 2 abnormal clones: 1 with the t(4;11) only, and a second with the t(4;11) plus additional chromosomes. The break points in the 9 patients studied with G-banding were q21;q23. Van den Berghe noted break points q13;q22 in his 3 cases who were studied using the R-banding technique. Two of our patients and 1 from the literature were analyzed sequentially, and 2 of these 3 showed karyotypic evolution over time.

Two of our patients and one from the literature were first studied after treatment, and all of them showed karyotypic abnormalities, both numerical and structural, in addition to the t(4;11). It is interesting to note that the two patients who had low peripheral leukocyte counts (4 and 7 \times 10^9/liter) were in this posttreatment group. The numbers are too small and the other abnormalities too varied to draw any conclusions about treatment-induced anomalies or clonal evolution at this time.

Six of our 7 patients and 2 of the 7 evaluable patients from the literature achieved an initial complete remission using conventional chemotherapy; however, the duration of first remission was very short (≤8 mo) in all but our case 7. Survival of this group as a whole has been dismal. In the 8 previously reported cases, survival ranged from 48 hr to 7 mo (median 3 mo). Four of our patients were dead from their leukemia by 16 mo after diagnosis despite aggressive chemotherapeutic treatment in all cases and allogeneic bone marrow transplantation in cases 3 and 6. Treatment given to our cases 1, 3, 4, and 5 was identical to that recently reported by the Childrens Cancer Study Group. Greater than 50% of poor prognosis patients treated in this fashion are surviving disease-free 5 yr after diagnosis. The only long-term survivor among the t(4;11) subgroup of ALL thus far is our case 7, who presents a problem in that he was not studied at diagnosis, and banding was not clear enough to definitely assign the q21 break point on chromosome 4.

Our data confirm and extend those from the literature suggesting that the t(4;11)(q21;q23) is a significant and specific karyotypic abnormality found in a subgroup of patients with non-T, non-B ALL. Patients with this anomaly at diagnosis present acutely with anemia, marked leukocytosis, and splenomegaly. The prognosis of these patients with optimal conventional chemotherapy is very poor, and an alternative approach to treatment appears indicated.

With further refinement of banding techniques other such subgroups of ALL will likely be uncovered. Correlation of the cytogenetic findings with more advanced histologic and immunologic studies, such as electron microscopy and monoclonal antibodies, will be important.

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