Clinical Aspects of Infant Leukemia—Experiences of a Single Institution of Japan: High Level of Serum Immunoglobulin M in Infant Leukemia

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Abstract

The prognosis and clinical and biological characteristics of infant leukemia differ from those of leukemia in children 1 year or older. We reviewed the charts of patients younger than 1 year in whom leukemia was diagnosed from January 1981 through December 2003 at our institution. Fourteen infants had leukemia, 6 had acute lymphoblastic leukemia (ALL), and 8 had acute myeloid leukemia (AML). The age of patients at diagnosis ranged from 2 to 11 months. Five of 8 AML patients presented with cutaneous manifestations, such as erythema and nodules, at diagnosis. Central nervous system (CNS) involvement was seen in 1 AML patient at diagnosis. Hyperleukocytosis of more than $50 \times 10^9$/$L$ was seen in 4 of 6 ALL patients and in 4 of 8 AML patients at diagnosis. All ALL patients showed a morphological diagnosis of L1 using the French-America-British classification system. For patients with AML, the morphological diagnoses were M0 for 1 patient, M2 for 1 patient, M4 for 2 patients (1 with eosinophilia), M5b for 2 patients, and M7 for 2 patients. One patient showing M7 morphology had Down syndrome. Surface markers were examined in 5 of 6 ALL patients and all AML patients. Five ALL patients showed a B-cell precursor immunophenotype. Two of 5 patients with ALL had CD10-positive leukemic cells and 3 of 5 patients with ALL had CD10-negative leukemic cells. All AML patients were positive for CD13 or CD33 or both. Three of 5 patients with ALL showed abnormal chromosomes related to 11q. Six of 7 patients with AML showed abnormal karyotypes. MLL gene rearrangements were seen in 3 (2 ALL, 1 AML) of 5 (2 ALL, 3 AML) patients. Serum immunoglobulin M levels were increased in 9 of 14 patients. Complete remission (CR) was achieved in all infants with ALL. Three patients relapsed and then died of the original disease. One of these 3 patients died after cord blood transplantation. Three ALL patients are alive without leukemia. CR was achieved in 6 of 8 AML patients. Four of 6 patients are alive without leukemia. Infant leukemia patients in our institution had some special features. CNS involvement at diagnosis was seen in only 1 patient and serum IgM levels were higher than those in children whose leukemia was diagnosed at 1 to 10 years of age.


Key words: infant, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, MLL gene
Introduction

Although the prognosis of leukemia in children has improved dramatically, leukemia in infants is still associated with poor outcomes\(^5\). In children younger than 15 years, childhood leukemia occurs in 3 to 4 per 1 million per year in Japan. Leukemia in infants younger than 1 year represents only about 7.5% of all childhood leukemias\(^6\). The incidence of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is different in children who are older than 1 year at diagnosis, with AML representing approximately 25% and ALL representing about 70% of all childhood leukemias. On the other hand, the incidence of AML and ALL are almost the same in infant leukemia.

The clinical and biological features of infant leukemia are different from those of childhood leukemia. For example, massive hepatosplenomegaly, central nervous system (CNS) involvement, and skin lesions are frequently present at diagnosis in infant leukemia\(^6\). Negative CD10 and MLL gene rearrangement are seen in infants with ALL more frequently than in children with ALL diagnosed at age 1 or older\(^6\). M4/M5 feature and t(9;11)(q23;q23) are seen frequently in infants with AML, but Auer body-positive leukemic cells or t(8;21) are seldom seen\(^6\).

We retrospectively analyzed patients with infant leukemia at our institution to re-evaluate its clinical and biological features.

Patients and Methods

Patients younger than 1 year with newly diagnosed leukemia treated at our institution from January 1981 through December 2003 were reviewed. Clinical presentation, laboratory findings at diagnosis, body weight and gestational age at birth, mothers’ condition during pregnancy, and outcome were reviewed using the patient’s chart to examine the clinical and biological features of infant leukemia. The diagnosis of ALL or AML was based on the characteristics of leukemic cells stained by the Romanovsky procedure and the reactivity of the cells to peroxidase staining and esterase staining. Standard morphologic studies and cytochemical staining properties of leukemic cells were performed according to the French-Amercia-British (FAB) classification system\(^1\). Cell surface antigen and chromosome studies were performed on bone marrow cells. Surface antigen expressions were examined using monoclonal antibodies against CD3, CD4, CD7, CD8, CD10, CD19, CD20, CD13, CD33, CD34, CD41, CD42, and HLA-DR by flow cytometry\(^2\).

MLL gene rearrangements were analyzed using Southern blotting\(^2\) in 2 of 6 ALL patients and 3 of 8 AML patients. Chromosomes were described according to convention of the international system for human cytogenetic nomenclature (ISCN 1995)\(^3\). Cytogenetic analysis was performed in 13 of 14 patients.

A lumbar puncture was done in all patients before the start of leukemia therapy. CNS leukemia was defined by the presence of leukemic cells (>6/L).

Overall survival and event-free survival (EFS) curves were prepared using the Kaplan-Meier method. Overall survival was defined as the time between the start of treatment and death. EFS was defined as the time from the start of complete remission (CR) to either death or relapse at any site.

Results

Patients

Fourteen patients younger than 1 year had leukemia. Six had ALL and 8 had AML. The median age at diagnosis was 5.8 months for patients with ALL (range, 2 to 11 months) and 8.0 months for patients with AML (range, 3 to 11 months). There were 7 boys and 7 girls (ALL 4 and 2, AML 3 and 5, respectively). There were 7 patients were found to have leukemia from 1981 through 1990 (4 ALL, 3 AML), 6 from 1991 through 2000 (2 ALL, 4 AML), and 1 from 2001 through 2003 (1 AML).

Body weight at birth was less than 2.500 g in 3 infants (1 ALL, 2 AML). Two infants were born before 37 weeks’ gestation.

Clinical and Laboratory Features

Table 1 shows the clinical and laboratory features
of all patients. At diagnosis, 7 infants had a fever (3 ALL, 4 AML), 2 had subcutaneous nodules (2 AML), 3 had erythema (3 AML), 1 had facial palsy (1 ALL), 1 had hemorrhagic tendency (1 AML), 1 had exophthalmos (1 AML), 12 had hepatomegaly (>4 cm below the costal margin; 4 ALL, 8 AML), and 10 had splenomegaly (>4 cm below the costal margin; 4 ALL, 6 AML). One patient had hemolytic uremic syndrome due to Escherichia coli O-113 1.5 months before the onset of ALL, and 1 ALL patient was referred to our institution with splenomegaly that was discovered at the 4-month medical check-up. CNS leukemia was found in 1 AML patient at diagnosis.

Hyperleukocytosis of >50.0×10^6/L (range, 61.7 to 264.0×10^6/L) was seen in 8 of 14 patients (4 ALL, 4 AML). Ranges of 50×10^6/L to 100×10^6/L were seen in 2 patients (1 ALL, 1 AML), and levels >100×10^6/L were seen in 6 patients (3 ALL, 3 AML). In contrast, a leukocyte count <0.5×10^6/L was seen in 2 patients (1 ALL, 1 AML). Blasts in peripheral white blood cells (WBC) were observed in 27% to 94% of ALL patients, and 0% to 88% of AML patients. Hemoglobin levels in all patients were less than 70 g/L. The platelet count was less than 50×10^9/L in 3 patients (1 ALL, 2 AML). Thirteen (5 ALL, 8 AML) of 14 patients had high lactic dehydrogenase levels. High lysozyme levels were seen in all 8 AML patients, but in no ALL patients. For patients in whom values were determined, ferritin levels >200 mg/L were seen in 7 (3 ALL, 4 AML) of 11 patients, high thymidine kinase activity was seen 3 (1 ALL, 2 AML) of 3 patients, and high neopterin activity was seen in 3 of 3 patients (1 ALL, 2 AML). Immunoglobulin (Ig) G, IgA, and IgM were examined in all patients. All three Igs were polyclonal antibodies. IgG levels ranged from 4.27 to 15.74 g/L in ALL patients (mean, 9.56 g/L) and 4.11 to 27.51 g/L in AML patients (mean, 10.56 g/L). IgA levels ranged from 150 to 1620 mg/L in ALL patients (mean, 620 mg/L) and 160 to 3,540 g/L in AML patients (mean, 1,110 g/L). IgM levels ranged from 940 to 5,240 mg/L in ALL patients (mean, 2,290 mg/L) and 570 to 7,750 mg/L in AML patients (mean, 2,970 mg/L) (Fig. 1).

**Conditions during Pregnancy**

We collected information on conditions during pregnancy in 13 mothers. Five of 13 had some problems during their pregnancy. Three of 8 received some type of drug therapy, including
nonsteroidal anti-inflammatory drugs for neuritis of the lumbar spine, iron therapy for 6 months for prolonged iron-deficiency anemia starting at the fourth gestational month, and antibiotic therapy against chlamydia. One mother had hydronephrosis and stenosis of the ureter. One mother had threatened premature labor.

**Morphology, Immunophenotyping, and Cytogenetics of Leukemic Cells**

In the FAB classification, all ALL patients showed L1; AML patients showed the following morphology: 1 was M0, 1 was M2, 2 were M4 (1 was M4 with eosinophilia), 2 were M5b, and 2 were M7.

Surface markers were examined in 13 patients (5 ALL, 8 AML). Three ALL patients had CD10-negative leukemic cells. Among AML patients, 6 of 8 were positive for CD13, 6 of 8 were positive for CD33, and 4 of 8 were positive for both CD13 and CD33. One patient who showed the M7 marker showed CD41, CD42, and HLA-DR cells in addition to CD33 cells. Another M7 patient (with Down syndrome) showed CD2 and CD5 cells in addition to CD13 and CD41 cells.

Twelve (5 ALL, 7 AML) of 14 patients underwent chromosomal studies. Three of 5 ALL patients showed abnormalities of chromosomes related to 11q. Six of 7 AML patients showed abnormal chromosomes. Trisomy of chromosome 8 was seen in 2 patients, abnormalities related to chromosome 6 were seen in 3 patients, and chromosome X appeared in 2 of 7 AML patients. The M7 patient without Down syndrome showed tetrasomy 21 and +6 and +8. The M7 patient with Down syndrome showed both tetrasomy and pentagonsomy 21, and monosomy 7. Inversion 16 was seen in M4 in the patient with eosinophilia. MLL gene rearrangements were analyzed in 5 patients (2 ALL, 3 AML) because the genetic analysis of leukemic cells was not required in earlier studies. Two ALL and 1 AML patient had positive MLL gene rearrangements (**Table 2**).

**Treatment and Outcome**

All patients received chemotherapy. ALL patients were treated using the modified Tokyo Children’s Cancer Study Group ALL protocol (TCCSG) L81-10 or L84-11 before 1989, and the Japan Infant
Table 2  Cytogenetic analysis of leukemic cells in infants with ALL and AML

<table>
<thead>
<tr>
<th></th>
<th>ALL (n = 5)</th>
<th>AML (n = 7)</th>
</tr>
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<tbody>
<tr>
<td>Normal karyotype</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abnormalities involving chromosome 11</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>t (4;11) (q21;q23)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>t (9;11)</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Abnormalities involving chromosome 6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Abnormalities involving chromosome 21</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Abnormalities involving chromosome X</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MLL gene rearrangement</td>
<td>2/2**</td>
<td>1/3***</td>
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</tbody>
</table>

* Breakpoints were not determined in this patient.
** Two patients were examined for MLL gene rearrangement.
Both showed MLL gene rearrangement.
*** Three patients were examined for MLL gene rearrangement.
One patient had MLL gene rearrangement without abnormalities involving chromosome 11.

Leukemia protocol during 1989 and 1995. After 1997, patients (2 patients) were treated using the MLL protocol\(^2\) including stem cell transplantation. AML patients were treated using the TCCSG81-10 Protocol for ANLL (cytarabine, doxorubicin, vincristine, prednisone, 6-mercaptopurine, and methotrexate) before 1988. Patients (4 patients) were treated using ANLL91\(^9\) from 1991 through 1998, and 1 patient was treated using AML99\(^9\) after 1999. Overall survival rates in both ALL and AML patients were 50.0% (Fig. 2). There were no significant differences in EFS between ALL and AML patients (Fig. 3). All ALL patients achieved CR once. One patient received cord blood transplantation during the first CR. Three patients relapsed (2 bone marrow, 1 bone marrow and CNS) and then died. To date, 3 patients have continued CR for 226 years, 19.0 years, and 6.5 years after the onset of leukemia. Six of 8 AML patients achieved CR, and 2 patients died of infections during initial therapy. Three of 6 patients relapsed (1 bone marrow, 2 bone marrow and CNS) and then 2 patients died. One patient, who had 1 instance of bone marrow relapse and 2 instances of CNS relapse, continued CR more than 3 years using chemotherapy and cranial irradiation after the second relapse. To date, 4 of 8 patients have continued their CR for 18.3 years, 17.3 years, 9.2 years, and 3.2 years.

Two ALL patients have short stature, and one was 3 SD shorter than the average Japanese woman. These two ALL patients had 18 Gy cranial irradiation at 2 years of age. One patient had leukoencephalopathy accompanied by secondary epilepsy and mental retardation. Two patients had chronic active hepatitis due to hepatitis C virus infection; however, hepatitis C virus disappeared in 1 patient treated with interferon alpha.

Discussion

We treated a total of 148 patients with leukemia (111 with ALL, 32 with AML, and 5 with chronic myeloid leukemia) from January 1981 through December 2003 at our institution. Fourteen patients were younger than 1 year and accounted for 9.5% of the total population. The ratio of ALL to AML was 6 : 8. Six of the 111 ALL patients (5.4%) were younger than 1 year, and this proportion was comparable to previously reported ranges of 2.5% to 5.0%\(^14\)^\(^7\)^\(^20\). Eight of 32 AML patients (25.0%) were younger than 1 year; this proportion was slightly higher than that of previously reported ranges of 6.0% to 14.0%\(^2^1\). The ratio of boys to girls was 7 : 7; the general trend is for the incidence in girls to slightly exceed that in boys\(^2^2\).

Subcutaneous nodules were found in 2 AML patients as the initial symptom (1 each with M4 and M5), and both nodules were revealed by biopsy to be infiltrating leukemic cells. Infiltration of the CNS is relatively common in M4 or M5 patients\(^2^3\)^\(^*\), but CNS involvement was observed in only 1 patient.
Fig. 2  Overall survival of 6 infants with ALL and 8 infants with AML. The curves were calculated with the Kaplan-Meier method. Although 1 patient with AML relapsed 12 months after diagnosis, she continued to be CR for more than 5 years after receiving chemotherapy.

Fig. 3  EFS of 6 infants with ALL and 8 infants with AML. The curves were calculated with the Kaplan-Meier method.
with M5 disease at the initial examination. Extramedullary leukemic infiltrates are relatively common in infants with AML and were observed in our study in 2 of 8 AML patients but not in ALL patients at diagnosis. Hepatosplenomegaly was found at the initial examination in 4 of 6 ALL patients and all 8 AML patients. Hepatosplenomegaly is considered to occur predominantly in infants with ALL who are positive for the MLL gene and in AML patients with M4 and M5. One of the 3 patients who was positive for MLL or translocation at 11q23 had hepatomegaly alone and one had splenomegaly alone. Hepatosplenomegaly was observed not only in patients with M4 and M5, but also in patients with all types of AML. Although this finding does not agree with previous reports, it is difficult to draw any conclusions because of the limited number of patients.

The most useful prognostic factors for pediatric leukemia are age and WBC count at onset. These variables may also play an important role in infants. In ALL patients in particular, the prognosis is worse when the onset occurs at <6 months compared with an onset at ≥6 months. Of the 3 (of 6) ALL patients who developed the disease at <6 months old, 2 died and 1 survived after receiving cord blood transplantation. Although 2 of 8 AML patients developed the disease at <6 months old, both of them are still alive. The prognosis is not good for either ALL or AML when the WBC count is ≥50 × 10⁹/L at diagnosis. Six of 14 patients showed leukocyte counts ≥100 × 10⁹/L. With respect to the WBC count at diagnosis, 2 of the 3 ALL patients with a count ≥100 × 10⁹/L died, whereas the patient who received cord blood transplantation remains alive. All 3 AML patients with a WBC count ≥100 × 10⁹/L at diagnosis died. It has been reported that leukocytosis at diagnosis is more common in infants with leukemia than in children 1 year or older.

The hemoglobin level at diagnosis was ≤70 g/L in 3 of 6 ALL patients and 4 of 8 AML patients, which is comparable with reported levels in children older than 1 year with acute leukemia. The platelet count in 1 of 6 ALL patients and 2 of 8 AML patients was ≤50 × 10⁹/L, and significant thrombocytopenia was uncommon.

The IgM level of normal infants is lower than that of older children, but the IgM level at diagnosis was ≥2,000 mg/L in 8 of 13 patients and was ≥3,000 mg/L in 5 of them. IgM levels are reported to rise, and ranges are 500 to 2,250 mg/L at diagnosis in children aged 1 to 10 years with leukemia. However, IgM levels in our infant leukemia patients increased significantly more than that. Thus, some kind of infection might be involved in the onset of infant leukemia as a second hit of leukemogenesis. We did not find any reports that discussed IgM levels in infant leukemia. IgG and IgA levels at diagnosis in our infant leukemia patients were higher than that of normal infants, but were almost the same as in children aged 1 to 10 with leukemia.

Infant leukemia has been described to originate from leukemic clones that appear in the fetal period. On the other hand, secondary leukemia due to topo-II inhibitor has a MLL gene rearrangement the same as in infant leukemia. Therefore, exposure to topo-II inhibitors during the embryonic period is suggested to be a cause of infant leukemia. Because the mothers of 3 of our patients were treated with either anti-inflammatory agents, long-term administration of iron preparations, or antibiotic therapy during pregnancy, a possible relationship between these drugs and the onset of infant leukemia should be investigated more thoroughly. Because our data were drawn from such a small number of patients, no conclusions can be drawn.

Two of the 4 CD10-negative ALL patients had translocation of chromosomes 4 and 11, whereas 1 of them also had translocation of chromosomes 9 and 11. As the prognosis of CD10 negative ALL patients is reported to be poor, 3 of our patients died and 1 patient who received cord blood transplantation survived. These results lead to the possibility that powerful treatments, such as hematopoietic stem cell transplantation, may be necessary for patients with CD10-negative ALL.

Although 3 ALL patients with recurrence died of their disease, 1 AML patient with late recurrence survived with chemotherapy alone, whereas 2 AML patients with recurrence died at an early stage.

Because treatment strategies have changed over our study period, it is difficult to evaluate the
prognosis. From the 1980s to the early 1990s, 13.1% to 56.0% of patients with ALL \(^{3,33,34}\) and 32.0% to 72.1% of patients with AML \(^{5,42}\) patients who were younger than 1 year were reported to have an EFS. At our institution, 50% of ALL patients and 50% of AML patients also survived without leukemia, and the proportions were similar to those published earlier. It is certain that more intensive treatment is required for ALL patients who are CD10 negative and show expression of the MLL gene. Which AML patients require intensive treatment cannot yet be determined, but 2 of our patients died of infection in the early stage of treatment, so attention should be paid to chemotherapy, especially during the early stage.

Infants with leukemia at our institution had some special features. Although CNS involvement is relatively common in infant leukemia, only 1 of our patients had CNS involvement at diagnosis. Furthermore, serum IgM levels at diagnosis in our patients were increased much more in children whose leukemia is diagnosed at 1 to 10 years of age. Future studies will focus on collecting additional data on serum IgM levels to determine the meaning of these increased levels in infant leukemia.

References


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