Cytogenetic Features of Infants Less Than 12 Months of Age at Diagnosis of Acute Lymphoblastic Leukemia: Impact of the 11q23 Breakpoint on Outcome: A Report of the Children's Cancer Group

By Nyla A. Heerema, Diane C. Arthur, Harland Sather, Vincent Albo, James Feusner, Beverly J. Lange, Peter G. Steinherz, Paul Zeltzer, Denman Hammond, and Gregory H. Reaman

Cytogenetic analyses of pretreatment bone marrows were performed at local institutions as part of Children's Cancer Group (CCG) protocol CCG-107 for infants less than 1 year of age with previously untreated acute lymphoblastic leukemia (ALL). Cytogenetic analyses from 39 patients (17 males and 22 females) were accepted after review. Several unique cytogenetic features were observed. Twelve patients (31%) had a t(4;11)(q21;q23) and had a significantly shorter event-free survival (EFS) than did the other patients with adequate cytogenetic analyses (P = .009). Five additional patients had an 11q23 breakpoint, not associated with 4q21. When EFS for these 5 patients was compared with that of the t(4;11) patients, even with these small numbers there was a strong, although not significant, suggestion that the t(4;11) patients have a reduced EFS (P = .09), indicating that the specific translocation, t(4;11)(q21;q23), and not an 11q23 breakpoint per se, may be associated with the poor prognosis of these infants. Structural abnormalities were present in 27 of 28 patients with abnormal karyotypes. A new recurring abnormality, t(5;15)(p15.1;q11) or t(5;15)(p15.3;q13), was identified in 3 patients (Arthur et al., Blood 70:274a, 1987 [abstr suppl 1]). Two females had structural abnormalities involving Xp11, a breakpoint rarely seen in ALL. Fourteen (36%) patients had a single structural abnormality, and 13 (33%) had complex karyotypes. No patients had hyperdiploidy with more than 50 chromosomes. Only normal chromosomes were observed in 11 patients (28%), and their outcome did not differ from patients with abnormal karyotypes. These cytogenetic abnormalities found in the leukemic cells of infants are clearly different from those in older children and adults, and may explain, in part, the unique biologic characteristics of infant ALL.

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Cytogenetic analyses of pretreatment bone marrows of patients with childhood acute lymphoblastic leukemia (ALL) have shown that the chromosomal findings have prognostic significance.1-8 Studies of infant ALL have shown that disease characteristics in this age group may be different from those in older children and adults, suggesting that the pathogenesis of infant ALL may differ from the development of ALL in childhood or in adults.9-13 Infants with ALL tend to have hepatosplenomegaly, leukocytosis, frequent central nervous system (CNS) involvement, and a poor outcome. The leukemic cells are often common ALL antigen (CALLA)-negative or CD10+. Infant ALL cells also may have unique cytogenetic characteristics, including a high frequency of chromosomal translocations, as well as aberrations with 11q23 breakpoints, especially t(4;11)(q21;q23). Most cytogenetic reports of infant ALL have combined all 11q23 breakpoints, regardless of the recipient chromosome; therefore, the significance of the particular recipient chromosome is not well understood. The recipient chromosome is known to be correlated with disease phenotype, with recipient chromosome breakpoints 4q21 and 1p32 found primarily in ALL, and 1q21, 2p21, 6q27, 9p22, 10p11, and 17q25 found in acute nonlymphocytic leukemia (ANLL), whereas 19p13 occurs in both ALL and ANLL.14 In addition to grouping all 11q23 breakpoints, all infant acute leukemias (both ALL and ANLL) are frequently compared, compounding the difficulty of interpretation of the significance of clinical and cytogenetic data. Additionally, few infants have hyperdiploidy with more than 50 chromosomes, a common finding of ALL in other age groups. Thus, the cytogenetics of infant ALL provide evidence of some biologic characteristics of this disease in infants.

A unique constellation of clinical characteristics has been associated with 11q23 aberrations, regardless of the age at which they occur.15-21 These clinical characteristics also tend to be the characteristics of infant ALL. They include leukocytosis; a unique immunophenotype that is usually CD19+, CD10+, HLA-DR+, indicating an early B-cell, frequent biphenotypic leukemia; hepatosplenomegaly; frequent CNS involvement; and a poor prognosis.

Because of the high frequency of adverse cytogenetic abnormalities in infant ALL, the relative significance of different abnormalities is not understood. To better define and understand the cytogenetics of infant ALL, the Children's Cancer Group (CCG) protocol 107, Intensive Chemotherapy for Infants with Acute Lymphoblastic Leukemia, required chromosome analyses at diagnosis. We now report on the cytogenetic findings, as well as some clinical correlations, of 39 of these infants, the largest series of cytogenetic studies of infant ALL reported to date.

MATERIALS AND METHODS

Cytogenetic analyses of leukemic cells at diagnosis, before treatment, were initiated as part of CCG protocol CCG-107, Intensive

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Chemotherapy for Infants with Acute Lymphoblastic Leukemia. Inclusion in the study required that the child be less than 12 months of age at diagnosis. This was a one-arm study using vincristine, prednisone, asparaginase, daunomycin, and systemic infusion of very high-dose methotrexate with citrovorum factors as CNS preventive therapy. Standard maintenance consisted of 6-mercaptopurine and methotrexate, with monthly vincristine and prednisone pulses for 2 years for females and 3 years for males. The study was open to patient entry from January 16, 1984 through March 15, 1987. Banded cytogenetic analyses of bone marrow or unstimulated peripheral blood obtained before treatment were performed at local institutions. The type of processing and banding was determined by the individual laboratories. Data forms and original karyotypes from all cases were centrally reviewed by at least two members of the CCG Cytogenetics Committee. Two original normal karyotypes were required for review of cytogenetically normal cases; and for abnormal cases, two original karyotypes of each abnormal clone were reviewed. Inclusion of a normal case required analysis of at least 15 normal metaphases. An abnormal clone was defined as two metaphases with the same additional chromosome(s) or the same structural abnormality or three metaphases missing the same chromosome(s).^2^ A minimum banding level of 340 bands per haploid set was required for inclusion of a case. Karyotypes were designated according to the ISCN (1991).^2^ Thirty-nine analyses were accepted after review, and they form the basis of this report. The reasons for not accepting cases were no specimen sent for analysis (12), inadequate specimen (18), no response from the laboratory to requests for review materials (12) or inadequate materials for review (5), too few metaphases (8), inadequate banding (5), and, in 1 case, an abnormality may have been constitutional [t(13q; 14q)].

**STATISTICAL METHODS**

Most of the statistical analyses used life-table methods. Life-table curves were based on the Kaplan-Meier estimate^34 and comparison of the log rank test and the log-rank test were used in some situations in which the numbers of patients in one or more of the comparison groups were very small.^2^ Stratified log-rank tests were sometimes used to access the independent significance of one factor after adjustment for another factor.^28^ Comparison of patient subgroups and association of patient characteristics were examined with $\chi^2$ tests for homogeneity.

Event-free survival (EFS) and survival from the time of study entry were the two primary life-table outcome indices that were examined. EFS was defined as the time to first occurrence of induction failure, relapse at any site, death, or second malignant neoplasm. For patients not experiencing an event, EFS was the time to last follow-up.

Comparability of the patients who had adequate cytogenetic results and those who did not was examined in two ways, i.e., by (1) testing for similarity of important patient characteristics in both groups and (2) comparing overall EFS outcome in both groups.

**RESULTS**

Of the 100 patients entered on CCG-107, cytogenetic analyses from 39 were accepted after review and are listed in Table 1. Eleven patients (28%) had only normal metaphases, 5 of whom were less than 6 months of age and 5 from 6 to 12 months of age. Twelve patients (31%) had a t(4;11)(q21;q23), 3 with additional abnormalities. Ten of these 12 patients (83%) were less than 6 months of age at diagnosis. An additional 5 patients (12.8%) had other cytogenetic abnormalities that included a breakpoint at 11q23; only 1 of whom was less than 6 months, 2 were exactly 6 months, and 2 greater than 6 months. Other recipient chromosomes were 19p13.3 and 9p22. There was also an insertion of 9p13-p22 in 11q23, a duplication of 17q13(q23), and a der(11) with unidentified chromat in 11q23. This last patient also had an unrelated clone with a del(7q;15p22). Eleven patients (28%) had abnormal karyotypes that did not include a breakpoint at 11q23. Among these were 3 patients with a t(5;15)(p15.1;q11) or t(5;15)(p15.3;q13).^2^ Two female patients had breakpoints in Xp11. Two patients had a +19; in 1, this was the sole abnormality, whereas the other also had a t(7;12)(q36;p12). The patient with a +19 as the sole abnormality was the only patient with abnormal chromosomes without a structural abnormality. One patient had a del(6)(q15q25), which recurs in ALL. The other 3 patients had structural abnormalities not previously reported in ALL; 2 of these had breakpoints in 1p1. None of the patients had hyperdiploidy with more than 50 chromosomes. Fourteen patients (36%) had a single structural abnormality involving one or two chromosomes, whereas 13 patients (33%) had more complex karyotypes, with involvement of three or more chromosomes in either structural or numerical anomalies. Eight patients (20.5%) had gains of chromosomes or markers in addition to structural abnormalities. In 6 of the latter, the numerical abnormalities were secondary rather than primary, because clones with only the structural abnormalities were present. The primary abnormality could not be established in the other 2 patients. Chromosome loss occurred in 2 patients, -8 in one and -10 in the other.

The 39 patients with adequate cytogenetic analyses were compared as to age, white blood cell (WBC) count, sex, race, hepatosplenomegaly or nodal involvement, hemoglobin, cell surface markers (B-cell markers CD24, CD23, CD19, and CD10 and T-cell markers CD2, CD5, CD3, and CD7), and French-American-British (FAB) classification with the 61 patients for whom cytogenetic results were not adequate or available. There were no important differences between the two groups of patients in any of these parameters except the institutional FAB classification, in which a higher frequency of L2 or L2/L1 was observed in the patients without adequate cytogenetic analyses. However, there was no difference in FAB type as determined by the central reference laboratory. EFS was very similar for these two groups of patients ($P = .57$), further suggesting that those for whom cytogenetics were available were representative of the overall CCG-107 population (Fig 1). With a median follow-up of 72 months for those still in continuous remission, the probability of EFS for all patients at 60 months was 31% (Fig 1). The estimated median EFS was 11 months. The estimated survival at 60 months was 41%, with a median survival time of 26 months.

Eleven patients were classified as having normal chromosomes at diagnosis. EFS for these patients was the same as for patients with abnormal cytogenetic results ($P = .84$, Fig 2).

A t(4;11)(q21;q23) was found in 12 of the 39 (30.8%) adequate cytogenetic analyses. The (t4;11) patients were more likely to be less than 6 months of age ($P = .01$) when compared with the rest of the patients with cytogenetic data.
Table 1. Cytogenetic Results of CCG-107 Patients

<table>
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<th>Patient No.</th>
<th>Karyotype Interpretation: ISCN</th>
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<tr>
<td>1-7</td>
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</tr>
<tr>
<td>8-11</td>
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<td>28</td>
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<tr>
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</tr>
<tr>
<td>39</td>
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Although not quite significant at a conventional statistical level, there was a tendency for t(4;11) patients to have WBC counts of greater than 100 × 10⁹/L (P = .09). Patients with a t(4;11) had a significantly worse outcome (P = .009, Fig 3); all patients with a t(4;11) have failed, with the median EFS only 7 months (range, 0 to 46 months), whereas the median EFS for the rest of the patients with cytogenetic data was 23 months, with a 44% probability of EFS at 60 months. Five patients had 11q23 breakpoints that did not involve chromosome 4; 3 of these patients have failed (at 5, 6, and 23 months), but 2 are still in first remission at 77 and 79 months. When EFS for these 5 patients was compared with that of the t(4;11) patients, although not quite statistically significant because of the small numbers, there was a trend
for the t(4;11) patients to have a worse EFS ($P = .09$, log-rank exact test, Fig 4).

A highly significant difference in survival of patients diagnosed at less than 6 months of age compared with those 6 to 12 months of age has been reported in earlier CCG studies. In this study, the same type of effect was seen for the entire study population of CCG-107 children with EFS at 60 months of follow-up equal to 20.8% for patients less than 6 months of age and 44.2% for patients ≥6 months of age ($P = .001$). In the subset of patients with cytogenetic data, a similar pattern was observed with EFS at 60 months of follow-up equal to 19.1% for patients less than 6 months of age and 41.4% for patients ≥6 months of age. When outcome of patients less than 6 months of age at diagnosis was compared as to presence or absence of a t(4;11), the comparison did not reach a conventional significance criterion for EFS difference ($P = .15$). However, all patients with t(4;11) have failed to respond, whereas 4 patients without a t(4;11) are still at risk at 53, 72, 84, and 87 months of follow-up. Again, statistical significance may be limited by the small number of patients. Only 2 patients with a t(4;11) were ≥6 months of age at diagnosis, making it difficult for meaningful statistical analyses, but one notes that both t(4;11) patients failed early (at 5 and 8 months) and 8 of the 16 without t(4;11) remain in first remission, again suggesting the significance of the prognostic effect of the t(4;11). There was no longer a difference in EFS when those patients who did not have a t(4;11) were compared by age less than 6 months or ≥6 months at diagnosis ($P = .46$, Fig 5). Furthermore, the frequency of t(4;11) in infants less than 6 months of age (10 of 21) compared with those ≥6 months of age (2 of 18) at diagnosis was highly significant ($P = .01$). To assess which of these two factors has the greater independent prognostic effect, a stratified analysis for each with adjustment for the categories of the other factor (using a stratified log-rank exact test because of the small numbers involved) was performed. These results showed that, although the prognostic effect of t(4;11) was attenuated, it still was significant after adjustment for age ($P = .04$). On the other hand, the effect of age was dramatically reduced after adjustment for t(4;11) status ($P = .48$). This suggests that, although t(4;11) status and age are strongly intercorrelated in this infant ALL population, the more important prognostic factor is t(4;11) status.

CCG-107 patients who had not achieved complete remission by day 14 had a worse outcome than patients who had achieved complete remission by day 14. Eight of 9 evaluated patients with a t(4;11) had achieved a complete remission by day 14. These 8 patients had a significantly worse disease-free survival ($P = .007$) than the rest of the patients with cytogenetic data who had achieved complete remission by day 14 (20 patients, Fig 6).

Considering all patients in the study, CALLA$^+$ was a favorable prognostic feature ($P = .05$). Twenty of the cytogenetically classified patients were evaluated for the presence of CALLA; 14 were CALLA$^-$, and 6 were CALLA$^+$. All 6 evaluated t(4;11) patients were CALLA$^-$; this difference in CALLA status approached significance ($P = .06$), even with this small number of patients. Patients with a t(4;11)(q21;q23) did not differ from the rest of the patients in any other clinical parameters, including sex (6 males and 6 females) and FAB morphology. All 12 patients with
EFS of children with ALL has dramatically improved over the last 20 years. However, there are still subsets of patients with this disease who have a poor prognosis, including those less than 1 year of age at diagnosis. Within this group of patients, parameters predicting good and poor response to treatment are needed. We have confirmed that the specific translocation t(4;11)(q21;q23) is a poor prognostic indicator in infants. The poor outcome of these infants appeared to be associated specifically with the t(4;11), rather than with a breakpoint at 11q23 per se, because, when EFS of patients with a t(4;11) was compared with EFS of patients with an 11q23 breakpoint without chromosome 4 involvement, the difference in outcome approached significance even with this small number of patients (P = .01). Abnormalities of 11q23 in general have been reported to occur more frequently in infants less than 6 months of age at diagnosis than in infants 6 to 12 months of age (P = .01). Abnormalities of 11q23 in general have been reported to occur more frequently in infants less than 6 months of age at diagnosis than in those 6 to 12 months of age at diagnosis,15,33 but in this study this occurred only for the specific translocation, t(4;11)(q21;q23). An 11q23 breakpoint per se did not show a clearly different frequency between age groups (P = .23). Ten of 21 (48%) cytogenetically analyzed patients less than 6 months of age at diagnosis had a t(4;11)(q21;q23), whereas only 2 of 18 (11.1%) patients 6 to 12 months of age had this translocation. In contrast, only 1 of 5 patients with a breakpoint at 11q23 without 4q21 involvement was less than 6 months of age at diagnosis had a t(4;11)(q21;q23), whereas only 2 of 18 (11.1%) patients 6 to 12 months of age had this translocation. In contrast, only 1 of 5 patients with a breakpoint at 11q23 without 4q21 involvement was less than 6 months of age at diagnosis. Previous reports have indicated that t(4;11) was associated with female sex.51,54 We were unable to confirm this, because there were 6 males and 6 females with a t(4;11) in this study, giving a 1:1 sex ratio. The sex ratio of all the cytogenetically analyzed patients was 1.3 females to 1 male.

Of the 5 patients with an 11q23 breakpoint without involvement of 4q21, 1 had a t(9;11)(p22;q23), previously reported as common in ANLL, especially FAB subtype M5 (acute monocytic leukemia), but also reported in ALL.9,33 The lymphoblasts of this patient were CD19+ and CD24+. The
confirming a lymphoid origin of the leukemia. One patient had an ins(11;9)(q23;p13p22), which may result in juxtaposition of the same genes as in the more common t(9;11)(p22;q23). This patient's cells similarly demonstrated an early pre-B phenotype (CD19+, HLA-DR+), confirming their lymphoid origin. There was 1 patient with a t(11;19)(q23;p13.3), previously reported as perhaps as common as t(4;11) in infant ALL. A fourth patient with an 11q23 breakpoint had a duplication of 11(q13q23), similar to the duplication reported by Katz et al., and larger than the dup(11)(q21q23) reported by Raimondi et al. The significance of these duplications is not understood, and no molecular studies have been reported in any of these patients. The fifth patient with an 11q23 breakpoint without involvement of 4q21 had unidentified chromatin at 11q23. This patient also had a derivative chromosome 9 with a breakpoint at 9p13, and a second unrelated abnormal clone with a del(7)(p15p22). He had no immunophenotypic evidence of mixed-lineage leukemia. Oligoclonality has been reported as a common feature in infant leukemia, particularly in patients with an 11q23 breakpoint. The two cytogenetic clones in this patient were the only evidence for biclonality in this group of patients.

In this study, 44% of the infants with adequate cytogenetic analyses had abnormalities involving 11q23. This is similar to the frequencies of 11q23 involvement in infant acute leukemia (AL), including both ALL and ANLL, reported by others. Abe et al. reviewed the literature of infant AL and found 48% of the patients to have aberrations of 11q23. Since Abe et al.'s report, cytogenetic findings of at least 113 cases of infant AL have been reported, 65 (49%) of which have had 11q23 breakpoints. This frequency may show some ascertainment bias because t(4;11) patients may be more likely to be reported than other patients. This study was multi-institutional and all patients with adequate cytogenetic analyses were included; thus, it may more accurately reflect the true incidence of the various cytogenetic abnormalities of infant ALL.

Recently, the genes involved in the t(4;11) translocation have been identified. The gene on chromosome 11 has been designated MLL and appears to be involved in many of the 11q23 chromosomal translocations, including t(4;11), t(6;11)(q27;q23), t(9;11)(p22;q23), t(11;19)(q23;p13.3), t(1;11)(p32;q23), t(10;11)(p11;q23), and del(11)(q23). Molecular studies of rearrangements of this gene in infant ALL have shown a much higher frequency of rearrangement (70% to 80%) of this locus than has been reported using cytogenetic studies. These studies also show the rearrangement in a higher frequency of infants less than 6 months of age (88%) compared with infants ≥6 months of age (58%) at diagnosis.

The gene on chromosome 4 has been designated AF-4. Leukemic cells with t(4;11) have altered RNA transcripts from both the derivative chromosomes 11 and 4, and two reciprocal fusion products coding for chimeric proteins.

**Figure 4. Comparison of EFS of CCG-107 patients with a t(4;11) and those with an 11q23 breakpoint without involvement of chromosome 4q21.**
derived from MLL and AF-4 are produced. This implies that 11q23 aberrations with different recipient chromosomes may result in different altered transcripts and oncogene fusion proteins. This is consistent with our finding that patients with a t(4;11) have a worse outcome than those with other 11q23 aberrations. This may result from different altered transcripts produced as a result of the various aberrations.

A breakpoint at 11q23 also has been associated with secondary leukemia, usually ANLL, particularly in patients previously treated with topoisomerase II-reactive drugs. The recipient chromosome in these patients also differs, with a t(9;11) frequently reported, but a t(4;11) also occurs. The 11q23 molecular breakpoint in two of these patients has been localized to the same region as the 11q23 de novo cases. The significance of the same chromosomal breakpoint in these two divergent groups of patients is not understood, nor is the relationship between infant ALL with t(4;11) and therapy-related ALL with t(4;11).

Several additional cytogenetic features were noted in this group of patients. Two female patients had structural abnormalities involving Xp11. Structural abnormalities of the X chromosome are rarely seen in ALL; and aberrations with an Xp11 breakpoint have been reported only twice previously, once in a 7-year-old female with t(X;14)(p11;q12) and once in a male infant with t(X;5;6)(p11;q12;q16). It is interesting that 3 of the 4 ALL patients reported with breakpoints in this region were infants, and that 2 of the patients had complex translocations involving three chromosomes.

Three patients in this study had a t(5;15)(p15.1;q11) or t(5;15)(p15.3;q13). This is a new translocation that, to date, has been reported only in infants. These patients are described in detail in a separate publication (Arthur et al, manuscript in preparation).

A high frequency of structural abnormalities has been reported in infant ALL. Only 1 of the 28 (4%) infants with abnormal chromosomes in CCG-107 did not have a structural abnormality, confirming that this age group has a high frequency of structural abnormalities and a concomitantly low frequency of only numerical abnormalities. In 6 of 8 patients with both structural and numerical abnormalities the structural abnormality was primary, because these patients also had a clone with only the structural abnormality, thus evidencing clonal evolution. Complex karyotypes were also frequent in these infants; 13 had three or more abnormal chromosomes. Both clonal evolution and complex karyotypic abnormalities have been associated with an aggressive clinical course.

Normal cytogenetics have been reported to occur more frequently in patients 6 to 12 months of age at diagnosis than in infants less than 6 months of age. In this study, normal chromosomes were found in similar frequencies in infants less than 6 months of age (24%) and those 6 to 12 months of age (33%) at diagnosis.

None of the infants reported in this study had hyperdiploidy with more than 50 chromosomes, a cytogenetic group associated with a good outcome. Only 3 infants less than 12 months of age with ALL and hyperdiploidy with...
Fig 6. Comparison of EFS of CCG-107 patients who had achieved a complete remission by day 14 and had a t(4:11) (---) and those who had achieved a complete remission by day 14 and did not have a t(4:11) (----). N. number of patients at diagnosis.

more than 50 chromosomes have been reported, although this abnormality is found in 21% to 49% of all childhood ALL patients. Undoubtedly, patients with hyperdiploidy with more than 50 chromosomes are a separate biologic subset of ALL, and this subset is rare in infants, partially accounting for the poor prognosis of infants with ALL.

Collectively, these cytogenetic data illustrate the heterogeneity of childhood ALL and demonstrate biologic differences that occur in this disease in infants compared with other children and adults. Thus, not only are there different biologic subsets of ALL, but the subsets occur in different frequencies in different age groups, with infants less than 1 year of age forming a unique group. The poor prognosis of infant ALL with current therapy may therefore be related to differences in the biologic properties of the disease in this age group.

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APPENDIX

Principal Investigators of the Children's Cancer Group (institution, investigator, grant no.): Group Operations Office, University of Southern California Comprehensive Cancer Center, Los Angeles, W. Archie Bleyer, Denman Hammond, Harland Sather, Mark Kralio, Jonathan Buckley, Madeline Bauer, Daniel Stram, Mae Won Lee, CA 13539; University of Michigan Medical Center, Ann Arbor, Raymond Hutchinson, CA 02971; University of California Medical Center, San Francisco, Katherine Matthay, CA 17829; University of Wisconsin Hospital, Madison, Paul Gaynon, CA 05436; Children's Hospital and Medical Center, Seattle, WA, Ronald Chard, CA 10382; Rainbow Babies and Children's Hospital, Cleveland, OH, Susan Shurin, CA 20320; Children's Hospital National Medical Center, Washington, DC, Gregory Reaman, CA 03888; Children's Memorial Hospital, Chicago, IL, Edward Baum, CA 07431; Children's Hospital of Los Angeles, CA, Jorge Ortega, CA 02649; Children's...
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Cytogenetic features of infants less than 12 months of age at diagnosis of acute lymphoblastic leukemia: impact of the 11q23 breakpoint on outcome: a report of the Childrens Cancer Group

NA Heerema, DC Arthur, H Sather, V Albo, J Feusner, BJ Lange, PG Steinherz, P Zeltzer, D Hammond and GH Reaman

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