Chromosomal Abnormalities and Their Clinical Significance in Acute Lymphoblastic Leukemia

Third International Workshop on Chromosomes in Leukemia

ABSTRACT

Three hundred thirty newly diagnosed patients were studied to determine the frequency and type of chromosomal abnormalities in acute lymphoblastic leukemia (ALL) and their clinical significance. Analyses of banded chromosomes revealed clonal chromosomal abnormalities in 218 patients (66%), including all cases of B-ALL; and 70% of non-T, non-B ALL; but only 39% of T-ALL (p < 0.001). Patients were classified into 10 groups according to karyotype: no abnormalities (34%), one of the following recurring structural abnormalities [the Philadelphia chromosome (12%), t(4;11) (5%), t(8;14) (5%), 14q+ (4.5%), 6q− (4%)] or, in the remaining cases with abnormalities, the modal number [<46 (5%), 46 (12%), 47 to 50 (8%), >50 (9%)]. Response to treatment (achievement of complete remission and remission duration) and survival differed significantly among chromosome groups (p < 0.002). The best responses were seen in patients with a modal number >50; the poorest responses were found in patients with the t(4;11) and t(8;14). Interestingly, survival for children and adults who had karyotypes with the same specific structural abnormalities [e.g., the Philadelphia chromosome or t(4;11)] was identical. Multivariate analysis demonstrated that the karyotypic pattern was an independent prognostic factor even when age, initial leukocyte count, and French-American-British (FAB) type were considered. We conclude that banded chromosome studies should be performed in all patients with ALL at diagnosis to identify those patients who have a pattern associated with a poor prognosis who may require more aggressive therapeutic approaches such as marrow transplantation.

INTRODUCTION

Cytogenetic analysis using banding techniques has been increasingly applied to the study of malignant disease in recent years. Among the malignant hematological diseases, CML and acute nonlymphoblastic leukemia have been most extensively evaluated. For acute nonlymphoblastic leukemia, the karyotype has been found to be of clinical use in terms of both carrying the diagnosis and predicting the clinical course. Since there had been only a few relatively small studies of banded chromosomes in ALL, the Third International Workshop on Chromosomes in Leukemia was organized to better define the chromogenetic abnormalities in ALL and to determine their clinical significance. The data obtained concerning the frequency of various chromosome abnormalities and some clinical correlations have been reported earlier (5). In this report, we summarize the major findings of this workshop, and we describe the results of further analysis of the data, including a more detailed evaluation of the chromosome abnormalities observed in patients with hyperdiploid cells and a comparison of survivals in children and adults with various cytogenetic subtypes of ALL.

PATIENTS AND METHODS

Patients. The series consisted of 330 newly diagnosed patients with ALL studied in 17 institutions. The diagnosis of ALL was made at each institution utilizing the criteria of the FAB classification (1). In 174 cases (53%), lymphocyte surface marker analyses were performed, including, as a minimum, sheep erythrocyte and surface immunoglobulin determinations.

For each patient, pretreatment clinical data collected included sex, age, physical findings (lymphadenopathy, splenomegaly, mediastinal mass, and CNS involvement), hematological parameters (hemoglobin, WBC, percentage of circulating blasts, platelet count, percentage of marrow blasts), FAB type and, when performed, lymphocyte surface marker class. For each patient, additional clinical data collected included initial induction treatment administered and response, duration of initial remission, and survival.

Chromosome Analysis. Banded chromosome studies were performed on material consisting of predominantly leukemic blasts in all cases prior to initiation of treatment. The source of material was bone marrow in 92% of cases and blood in 8% of cases. In 63% of cases, direct preparations were studied; the material studied had been cultured without stimulation for 24 hr in 28% of cases, for 48 hr in 7% of cases, and for 72 hr in 2% of cases.

Chromosome abnormalities were designated using the short version of the nomenclature of the 1971 Paris Conference (3). For purposes of this study, an abnormal clone was defined as 2 or more metaphase cells with identical structural anomalies or identical extra chromosomes or 3 or more metaphases with identical missing chromosomes. A normal clone was considered to be present if only one mitosis was cytogenetically normal. For the leukemia to be considered totally normal cytogenetically, at least 5 metaphase cells from bone marrow had to have been examined and found to be normal.

Patients were divided into 10 groups based on chromosome findings. Patients were first classified according to the presence or absence of a clonal chromosome abnormality. Among patients with abnormalities, 5 recurring structural abnormalities were identified and used for grouping patients: (a) the Ph1, usually as a result of a 9q−:22q− translocation; (b) structural abnormalities of No. 8, most commonly an 8q−:14q+ translocation; (c) additions to the long arm of No. 14 (14q+) of other derivations; (d) the 4q−:11q+ translocation; and (e) a deletion of the long arm of No. 6 (6q−). The remaining patients with chromosome abnormalities were divided somewhat arbitrarily by modal chromosome number into 4 groups: (a) hypodiploid (<46 chromosomes); (b) pseudodiploid (46 chromosomes); (c) hyperdiploid A (47 to 50 chromosomes); and (d) hyperdiploid B (>50 chromosomes). The number of patients within each category is indicated in Table 1.
Statistical Methods. Clinical findings at diagnosis were compared among the different cytogenetic groups. Hypotheses of no difference were tested (at \( \alpha = 0.05 \)) by use of the Pearson \( \chi^2 \) statistic for 2-way frequency tables (discrete variables) and by use of the rank test of Kruskal and Wallis (for continuous variables). Durations of initial remission and survival of the various chromosome groups were plotted from life tables, calculated by the method of Kaplan and Meier. Since 33\% of the patients were still in remission and 46\% alive at the time of analysis, differences in remission duration and survival were tested for groups of at least 5 patients by use of the rank test of Kruskal and Wallis as modified by Breslow for application to censored data.

To study the prognostic value of various combinations of risk factors, models of multiple survivorship were examined. The method used was that of A. I. Goldman with expected survival expressed as an exponential function of the risk variables (2). In each model, survival was estimated by maximizing the likelihood function. Models that used different combinations of risk factors were compared, and the prognostic value of adding one or more factors was evaluated in terms of the increase in the maximized log-likelihood function. Such increases in likelihood functions are asymptotically distributed as 0.5 \( \chi^2 \) with the degrees of freedom given by the differences between the number of variables included in the 2 models. The increase in log-likelihood may thus be used as a \( \chi^2 \) statistic to test the prognostic value of a factor when controlling for the effect of other risk factors.

RESULTS

Cytogenetic Findings at Diagnosis

Clonal abnormalities were identified in 65.8\% of the cases. The frequency of abnormal karyotypes differed among immunological classes of ALL. An abnormal clone was identified in only 39\% of T-ALL (sheep erythrocyte positive) as compared to 70\% of non-T, non-B ALL (erythrocyte negative, surface immunoglobulin negative) and 100\% of B-ALL (surface immunoglobulin positive) (\( p < 0.001 \)).

Cytogenetic characteristics of each of the 10 karyotype categories described above were evaluated with an emphasis on the major patterns of aberrations within each group, defined as those present in at least 20\% of the members in each category. In these patients with complex karyotypes and less than ideal banding patterns, errors in analysis are bound to occur. Many of the karyotypes had a number of unidentified markers so that the origin of the chromosomal material that was gained or lost could not be determined. Patients with modal numbers greater than 50 were probably underrepresented because of the difficulty of identifying all of the chromosomes or of defining the markers, with consequent exclusion of these cases from the Workshop. Nonetheless, certain distinct patterns emerged.

Ph\(^+\)-positive Cases. Of the 39 patients in this group, 28 had pseudodiploidy; 3 each had 45, 47, or 51 to 55 chromosomes; and 2 had >56 chromosomes. The chromosomes involved in the Ph\(^+\) translocation were identified in 37 cases; in 34, the typical t(9q+;22q-) was noted. Variants included t(6p+;22q-), t(21q+;22q-), and t(3p+;9q+;22q-). The incidence of variant translocations was 5\%, which is similar to the 7\% frequency seen in Ph\(^+\)-positive CML.

Complete karyotyping was possible in 35 patients. Fifteen patients had the Ph\(^+\) translocation as their only abnormality, including 2 patients with variant translocations. One patient had 2 distinct clones, one t(9q+;22q-) and the other t(7q). Ten patients had only one clone, but abnormalities in addition to the Ph\(^+\). These were quite variable including a gain of chromosomes 8, 11, or 16 each in 2 patients; a loss of chromosomes 7 or 8 in each of 2 patients; and an isochromosome 7q(t(7q)) in 2 other patients. Other structural rearrangements or translocations were rare. Eight patients had at least 2 clones which were clearly related. The most frequent evolutionary change was an extra Ph\(^+\) seen in 4 of the 8 patients. The other changes usually seen in the blast crisis of CML were absent; only one patient had a +8, and no patient had an i(17q) or +19.

Abnormalities of Nos. 8 and/or 14. These 2 groups included 14 patients who had a t(8q-;14q+)(8q24;9q32); 2 who had a translocation involving No. 8 (break in 8q23-24) and some other chromosome; and 15 patients who had a 14q+ chromosome that, with one exception, did not involve No. 8. Of 16 patients with a t(8q-;14q+) or an 8q+, 15 had a pseudodiploid number. The modal number was more variable in the patients with a 14q+ chromosome, only 7 of whom had pseudodiploidy. Similarly, fewer additional chromosome changes were noted in the t(8q-;14q+) or 8q+ patients than in the 14q+ patients. Eight patients with the t(8q-;14q+) had only this abnormality, and 5 had only one or 2 other rearrangements. Only one patient with a translocation to 8q23-24(8q+) had a second structural rearrangement. Although patients with structural rearrangements of 8q were not specifically selected for this group, the only other patient with aneuploidy and a rearrangement involving No. 8 was one with a variant t(8q-;14q+) described below.

The karyotypic pattern in the 14q+ group was more complex; one patient had a t(8q-;14q+), but the breakpoints in both chromosomes differed from those in the previous group, i.e., 8q21 and 14q24. For 9 of the patients, the donor chromosome involved in the translocation to No. 14 was not identified. Four had a t(11q-;14q+)(q23;q32) and one had a t(10p-;14q+); this was the only abnormality in the latter patient. The other patients had additional changes including a gain of No. 7 or No. 13 each in 2 patients and an i(7q) in one other; loss of No. 9 or No. 13 each were noted in 2 patients. t(4q-;11q+). This abnormality was unique in that it occurred as the only abnormality in the cells of 17 of 18 patients. One patient had a deletion of the short arm of chromosome 17. The breakpoint in No. 4 appeared to be the same in all cases, namely, 4q21; the breakpoint in 11 usually occurred in 11q23 (14 cases), but other sites on the long and short arm were also involved.

6q-. The 13 patients in this group included every patient whose karyotype had a 6q- except for one patient with a 14q+ who also was 6q-; this patient was categorized as 14q-. Seven patients had 46 chromosomes; modal numbers for the others ranged from 47 to >60. Four patients were only 6q-. The breakpoint in the long arm of No. 6 varied from 6q15 to 6q25, but it tended to concentrate in 6q21. Other abnormalities associated with the 6q- were a +21 in 3 patients and +4, +10, +11, and +14 each seen in 2 patients. Two patients also gained both an X and a Y, and one female was +X. Losses and balanced translocations were rare; other variable rearrangements occurred in 9 patients.

Hypodiploidy. The majority of the 17 patients had 44 or 45 chromosomes in their leukemic cells. The chromosomes lost from these patients were variable. In 4, the loss involved a sex chromosome, an X chromosome in 2 adult females and a Y chromosome in 2 adult males. Loss of the Y chromosome was
the sole abnormality observed in the 2 males, ages 32 and 50 years. Loss of No. 9 occurred in 3 patients and loss of No. 21 occurred in 2.

Four patients had cells with a very low chromosome number, 27 to 36. Two of these had single clones, and 2 had a second clone with twice the number of chromosomes as the near-haploid clone. These 4 individuals with a near-haploid karyotype showed a remarkably consistent pattern. Two female patients, one a child and one an adult, had 27 and 28 chromosomes, respectively. In addition to a haploid karyotype, they both were +21, +21, and then +6. Two male patients, one child and one adult, had 35 and 36 chromosomes, respectively. They had both X and Y, the same consistent additions, namely, +10, +18, and +21, and they were both +1, +5, +6, +11, +19, and +22. Except for one patient, no structural rearrangements were noted.

Pseudodiploidy. In this group of 41 patients, the chromosome changes were relatively variable. The only chromosome gained in more than a single patient was No. 21 which was present in 3 patients. The following chromosomes each were lost in 2 patients, an X, an 8 or a 10, and a 12. Chromosome rearrangements involved No. 1 or No. 7 each in 4 patients; Nos. 2, 11, and 14 were affected in at least 2 patients. Chromosome No. 9 was uninvolved in deletions but was present in 7 balanced translocations. The long and short arms of No. 9 were affected with about equal frequency; in 3 patients, the same arm of both No. 9's were involved in the translocation event. With one exception, all 6 translocations affecting No. 1 involved the long arm. Other balanced translocations occurred in 9 patients.

Hyperdiploidy A (47 to 50 Chromosomes). Twenty-eight patients were found in this group. Twenty-two of the patients had 47 chromosomes, 2 had 48 chromosomes, and 4 had 49 chromosomes. The most common single change was a +21 seen in 7 patients; +13 was seen in 4 patients, and +4, +8, +18 each were present in 3 patients (Chart 1). No single chromosome was lost in more than 2 patients. There were relatively few structural rearrangements and, except for i(1q) which occurred twice, all aberrations were unique. Only 4 balanced translocations were identified, and each was different.

Hyperdiploidy B (>50 Chromosomes). This group contained 31 patients; 19 had 51 to 55 chromosomes, and the remainder had 56 to 92 chromosomes. Twenty-two patients had unidentified markers and 8 had other rearrangements; each was different except for +18q− which was noted in 2 patients. No translocations were identified. As in hyperdiploid Group A, +21 was the most common change, it was seen in 21 patients; this was especially notable in children since +21 occurred in 19 of 22 children (Chart 1). Other common extra chromosomes in order of decreasing frequency were +6 in 14, +18 in 13, +14 in 11, +4 in 10, and +10 in 9. Eight patients each had +13, +15, or +17. Eight patients (6 males, 2 females) also had an extra X chromosome; +Y was not seen.

Some differences emerge when one compares the 2 hyperdiploid groups; thus, although gains of 21 and 18 are common in both, other gains are seen almost exclusively in patients with over 50 chromosomes. For example, +6 was seen in 15 patients with >50 chromosomes and in none of the 28 patients with 47 to 50 chromosomes; +10 was seen in 9 of the former and in only one of the latter group; +14 was seen in 11 and one, respectively. If one compares the chromosomes commonly added in the >50 group with those added in the 4 patients with the near-haploid complement, the similarities are remarkable, since the most consistent in the latter are +10, +18, +21, and then +6.

Constitutional chromosome abnormalities were seen in 7 patients (2.1%); this is at least 4 times the expected frequency based on the incidence in the general population of 0.5%. The most common abnormality was Down's syndrome (+21) seen in 4 children, the 2 younger ones, ages 1 and 3 years, had no other abnormalities. The 2 older ones, 9 and 15.5 years, had a pseudodiploid karyotype with a 14q+ chromosome and other variable abnormalities. One 6-year-old child with the constitutional karyotype 47, XXY (Klinefelter's syndrome) had a +19. The 2 adults had balanced translocations, one a constitutional t(4p+:14q−) and +8, and the other a t(13q;14q) along with a t(q9;22q−) and −8.

Clinical and Hematological Characteristics According to Karyotype

The patients studied ranged in age from less than 1 year to...
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69 years; the median age was 16. The median age is high because some of the participating institutions treat only adult patients. Data regarding the total number of patients with ALL seen by these institutions during the time period of this study were not available. However, the clinical and hematological characteristics of the patients appeared to be typical of other published ALL populations.

Differences in presenting clinical and hematological features were found among chromosome groups. The findings are summarized in Table 1. The significant differences at diagnosis among the chromosome groups related to age (p < 0.001), frequency of CNS involvement (p = 0.003), WBC (p < 0.001), percentage of circulating blasts (p < 0.001), and distribution of FAB types (p < 0.0001) and lymphocyte surface marker characteristics (p < 0.0001). Patients with a 6q− and a modal number >50 were younger, and those with the Ph + and the 14q+ older than patients with other abnormalities. CNS involvement at diagnosis was more common in the t(8;14), the t(4;11), and the 14q+ groups. Patients with a t(4;11) had substantially higher initial leukocyte counts than did patients in other groups. Median presenting leukocyte counts were also high in the pseudodiploid, hypodiploid, and Ph + groups. The same 4 groups tended to have higher percentages of circulating blasts. Almost all cases of t(8;14) were FAB L3; the pseudodiploid and hypodiploid groups had the highest frequency of FAB L2. Striking differences in distribution of lymphocyte surface marker characteristics were also seen. Almost all patients in Groups 47 to 50, Ph +, and t(4;11) had non-T, non-B ALL; all cases of t(8;14) and a substantial fraction of 14q+ cases had B-ALL. The normal, pseudodiploid, and 6q− groups had a sizable fraction of T-ALL.

Response to Treatment and Survival According to Karyotype

Karyotype correlated with response to treatment and survival. Overall, 78% of patients achieved complete remission. Response rates varied among chromosome groups (p < 0.0001). The highest response rates were seen in patients with normal karyotypes and a modal number >50; the lowest were seen in patients with a Ph+, a 14q+, and t(8;14) (Table 1). Karyotype also identified groups of patients with different durations of initial complete remission [p < 0.002 (Chart 2)]. Remissions were longest in patients with a modal number >50 and shortest in those with t(4;11) or t(8;14). Similarly, significant differences in survival were seen according to karyotype (Chart 3).

Studies of survival in ALL have consistently demonstrated that children survive longer than do adults. Consequently, the influence of karyotype on survival was evaluated separately for children and adults. For those chromosome groups based on modal number, children survived significantly longer than did adults (Chart 4). However, for those chromosome groups based on specific translocations, survival was identical for children and adults (Chart 5).
Influence of Karyotype on Survival When Other Risk Factors Are Considered

Studies of survival in ALL have most consistently identified age and WBC at diagnosis as the major prognostic (or risk) factors. In addition, recent studies have suggested that the FAB classification and lymphocyte surface markers may be important risk factors. To determine the influence of karyotype on survival when other risk factors were considered, multivariate models of survivorship were compared. These analyses were limited in part by sample size.

As a first step, we evaluated various combinations of risk factors, other than karyotype, including age, WBC, percentage of circulating blasts, mediastinal mass, CNS leukemia, FAB types, and lymphocyte surface marker characteristics, which have been reported to have prognostic significance, to see which combination of risk factors best predicted survival. For only 152 patients was there information on all of these factors including lymphocyte surface markers, but for 277 patients there was information on the remaining factors. Thus, these latter 6 risk factors were considered. Age and WBC were grouped into previously identified prognostic classes as shown in Table 2. As indicated, each risk factor was treated as a continuous or binary variable. The multiple survivorship model containing all 6 risk factors effectively predicted survival (i.e., was significantly better for estimating survival than was the model which assumed that all patients had the same hazard). However, only age, WBC, and FAB contributed significantly to the model (each \( p < 0.05 \)). The model containing only these 3 risk factors predicted survival in a fashion similar to the model with all 6 factors.

To determine if karyotype added significant prognostic information to age, WBC, and FAB, karyotypes were grouped as described earlier and coded as a series of binary variables.
Table 3
Multivariate analysis of the prognostic significance of karyotype for survival

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>Models tested (B-A)</th>
<th>$G^2(B)$</th>
<th>d.f.</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age, WBC, FAB</td>
<td>1-0</td>
<td>58.08</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Karyotype</td>
<td>2-0</td>
<td>56.08</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>Age, WBC, FAB, karyotype</td>
<td>3-1</td>
<td>36.56</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$d^2$ $G^2(B)$ is the $x^2$ statistic for testing the significance of the improvement in fit of adding the variables which are in Model B but not in Model A.

$$G^2(B) = 2[\ln L(\hat{\theta}_B) - \ln L(\hat{\theta}_A)]$$

where $\ln L(\hat{\theta}_B)$ is the maximized log-likelihood for Model B, and $\ln L(\hat{\theta}_A)$ is the maximized log-likelihood for Model A. Model 0 assumes that the hazard is the same for all patients.

Karyotype was first examined for its ability to predict survival among the 289 patients that had complete information on age, WBC, and FAB. As shown in Table 3, karyotype (Model 2) effectively predicted survival ($p < 0.001$). To determine if karyotype was an independent prognostic variable, the model containing karyotype, age, WBC, and FAB (Model 3) was compared to the model (Model 1) containing only age, WBC, and FAB. Karyotype added significant prognostic information to age, WBC, and FAB ($p < 0.001$ (Table 3)). Thus, karyotype appears to be a prognostic variable independent of the other known risk factors in ALL.

DISCUSSION

In this study, 66% of cases of ALL demonstrated clonal chromosome abnormalities. Since only 5 metaphase cells obtained from bone marrow using direct techniques were required for a case to be considered normal, this may represent a low estimate of the frequency of clonal abnormalities in ALL. More cells should probably be examined to conclude that a case is normal. Moreover, recent data indicate that, using standard banding techniques, 24- to 48-hr culturing of cells from myeloid disorders is more likely to detect abnormalities than is direct preparation. Whether a similar phenomenon occurs in malignant lymphoid diseases is unclear. However, the workshop data tend to suggest that it does because, among marrow specimens studied, 41% of direct preparations were normal as compared with 36% of 24-hr preparations and 27% of 48-hr preparations. It is of interest that all B-ALL and 70% of non-T, non-B ALL had clonal abnormalities, but this occurred in only 39% of T-ALL. This could be a function of current techniques which may favor divisions from the nonmalignant cells rather than T-lymphoblasts. Alternatively, chromosome abnormalities in T-ALL may be too small to be detected with routine banding techniques, or chromosome abnormalities may less often be involved in T-ALL than they are in other immunological types of ALL.

The Third International Workshop study was the first to demonstrate that karyotype is an important independent risk factor in ALL (5, 6). Karyotype significantly correlated with achievement of complete remission, duration of complete remission, and survival. Why these cytogenetic abnormalities correlate with response to treatment and survival is unknown. However, our data suggest that karyotype is an independent risk factor since it correlated with survival even when other major risk factors in ALL, such as age, WBC, FAB type, and probably lymphocyte surface markers (5) were considered. A larger series of ALL studied with lymphocyte surface markers and karyotypic analysis is required to better define the relation of lymphocyte surface markers and karyotype.

Patients with ALL with a modal number >50 respond best and children frequently appear to be cured. Patients without chromosome abnormalities or a 6q- also do well. In contrast, patients with t(4;11) or t(8;14) ALL respond particularly poorly and have the shortest survivals.

Karyotype, when classified as in this study, frequently had different prognostic implications in children and adults. However, when specific cytogenetic types of ALL were identified [i.e., t(9;22), t(4;11), and t(8;14)], the survival curves were superimposable for children and adults. This is of some interest since karyotype may be the first biological marker to identify a type of ALL which has comparable survival in children and adults. In all the less specific cytogenetic groups, survival was better for children. This suggests that children and adults may have cytogenetically different leukemias included within the cytogenetic groups based on modal number, the 14q+, the 6q-, and “no” chromosomal abnormalities. Preliminary analysis suggests that such may be the case. Our data suggest that, when (and if) specific chromosome abnormalities are identified within these broad chromosome groups, the response in children and adults will be identical for patients with the same karyotype. Study of more cases using additional and more refined cytogenetic techniques will hopefully identify additional karyotype subgroups of ALL.

Although this study has clearly identified prognostic groups in ALL, further follow-up is required to correlate specific chromosome findings with cure. A large multiinstitutional prospective study reporting cytogenetic findings in all ALL patients presenting to the institution (whether karyotyping or banding were successful or not) and including central FAB review, extensive immunological phenotyping, and other biological markers, as well as optimal therapy, would be of major interest and is being discussed among workshop participants.

Although further study is required, our data indicate that karyotype is an independent prognostic factor in ALL. Consequently, karyotype must be considered in designing clinical trials in ALL. Whether new approaches to treating patients in poor-prognosis cytogenetic groups will improve their chance for cure needs to be explored. However, to provide patients with the most accurate information regarding prognosis, banded cytogenetic analyses should be performed on all patients with ALL at diagnosis.

REFERENCES


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