A Retrospective Cytogenetic Abnormality in Pediatric Acute Lymphoblastic Leukemia: Report of 11 Years

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Abstract

Background: Acute lymphoid leukemia (ALL) is the largest subset of hematologic malignancies, accounting for approximately 70%–80% of childhood leukemia, and is most common at age 4 years. The aim of this study was to define the frequency of chromosomal abnormalities in pediatric ALL.

Materials and Methods: In this 11-year retrospective study, we investigated 99 patients who referred to our department due to ALL from 2010 to 2020. The age group of the patients ranged from 6 months to 14 years with a mean of 6.71 ± 4.09 years. Clinical and diagnostic findings were extracted from patients’ medical records.

Results: We showed cytogenetic abnormalities of 99 pediatric ALL patients, including 78 pre-B-ALL, 9 common B-ALL, and 12 T-ALL cases. The 5-year overall survival rate (OSR) and event-free survival (EFS) of all cytogenetic abnormalities (n = 99) were 48% and 43%, respectively. There was a significant relationship between the two cytogenetic abnormalities, hypodiploidy and t(9;22), with death (P < 0.05). On comparing the subjects with normal cytogenetics to the other cytogenetic abnormalities, EFS was significantly low for hypodiploidy (P = 0.0163, hazard ratio = 0.5308) and t(9;22) (P = 0.0131, hazard ratio = 0.4908), while other cytogenetic abnormalities did not have a statistically significant difference in EFS.

Conclusions: Our results emphasized the importance of the cytogenetic findings in evaluating the survival outcomes, which allows identifying a variety of OSR and EFS, because some of the cytogenetic abnormalities may interfere with the death and prognosis.

Keywords: Acute lymphoblastic leukemia, cytogenetic abnormalities, karyotype, overall survival

INTRODUCTION

Leukemia is the most common form of cancer in children under the age of 15, accounting for about 30%–45% of childhood cancers.[1,2]

Acute lymphoid leukemia (ALL) is the largest subset of hematologic malignancies, accounting for approximately 70%–80% of childhood leukemia, and is most common at age 4 years. The sixth most common disorder in Iran is ALL and its annual incidence in some provinces of Iran reaches 3.7/100,000 population.[3]

The overall survival rate (OSR) in developed countries is reported to be between 30% and 70%. However, OSR in the Western population has reached more than 85%.[4]

Genetic and epigenetic disorders occur in most patients with ALL as well as in acute myeloid leukemia. These chromosomal...
disorders, which may present as translocations, duplications, deletions, inversions, and methylation, provide valuable information about the prognosis and the diagnosis of the disease. These disorders also affect gene expression and alter the normal programs of cell differentiation, proliferation, and survival. In recent years, epigenetic disorders including methylation of tumor suppressor genes have also been revealed to play a role in ALL pathogenesis. Aneuploidy and numerical chromosomal alterations occur frequently in patients with ALL. Identifying the frequency of chromosomal abnormalities in children with ALL in each region plays a major role in determining the prognosis of the disease. Chromosomal abnormalities provide valuable information about the prognosis of the ALL.

Given that the prevalence of ALL is somewhat affected by diagnostic and reporting differences, this study aimed to evaluate the frequency of cytogenetic abnormalities and the percentage of frequencies based on age and sex in children with ALL in Markazi Province with respect to OSR and event-free survival (EFS).

**Materials and Methods**

**Patients**

In this 11-year retrospective study, we studied all the leukemic patients referred to the Cytogenetic Laboratory of Amirkabir Hospital, Arak University of Medical Sciences, Arak, Iran, for chromosomal analysis during 2010–2020. The age group of the patients ranged from 6 months to 14 years with a mean of 6.71 ± 4.09 years.

Clinical and diagnostic findings consisting of demographic data (age and gender), cytogenic abnormalities, karyotype, mediastinal mass breast (MMB), clinical outcome (includes complete remission [CR], overall survival, EFS, relapse, and death), white blood cells (WBCs), platelets (PLTs), hemoglobin (Hb), peripheral blood blasts (PBB), and lactate dehydrogenase (LDH) were extracted from patients’ medical records.

CR is defined with <5% blast cells in the bone marrow and correction of blood cell count (neutrophil count more than 1000 cells per microliter, PLT count more than 100,000 cells/microliter, Hb more than 10 g/dl, while the absence of blast cells in peripheral blood); furthermore, bone marrow cellularity more than 20% should provide evidence on hematopoesis of three cell lineages. EFS was defined from the time of CR to the time of death or relapse. OSR was defined from the time of diagnosis to the time of death for any reason.

The inclusion and exclusion criteria

Inclusion criteria included the following: definitive diagnosis of ALL using cytochemistry, morphology, cytogenetic analysis, and flow cytometric analysis. Study exclusion criteria included patients without evaluable cytogenetics, initiation of chemotherapy, acute adult leukemia, acute congenital leukemia, other cancers and genetic abnormalities, and unwillingness to participate in the study. Clinical and diagnostic findings were extracted from patients’ medical records.

**Statistical analysis**

SPSS software (version 16, Chicago, IL) was used for statistical analysis. Pearson’s Chi-squared test (or Fisher’s exact test) and Student t-test were utilized for qualitative variables and quantitative variables, respectively. A log-rank test was used to study the relationship between cytogenetic abnormality and survival rate. The multivariate logistic regression model was carried out to assess variables that might have influenced the OSR and EFS.

Kaplan–Meier tests were used for survival analysis and compared by the log-rank test. If the P value is 0.05 or lower, the result is considered significant.

**Ethical standards**

This study was approved by the Ethics Committee (ethical committee code number: IR.ARAKMU.REC.1399.171).

**Results**

A total of 221 patients with ALL under the age of 15 were evaluated. Cytogenetic analysis was available for 99 ALL patients. We showed cytogenic abnormalities of 99 pediatric ALL patients, including 78 (78.8%) pre-B-ALL, 9 (9%) common B-ALL, and 12 (12.2%) T-ALL cases. According to the age range of patients, five patients (5%) belonged to the age group under 1 year, followed by 1 to 10 years (80 patients, 81%) and more than 10 years (14 patients, 14%).

Miscellaneous subgroup comprised 10 patients with mosaic Down syndrome, trisomy 21, monosomy 7, inversion 16, and t(8;12). Laboratory findings based on cytogenetic abnormality are shown in Table 1.

The 5-year OSR and EFS of all the cytogenetic abnormalities (n = 99) were 48% and 43%, respectively. The 5-year OSR for B-ALL and T-ALL abnormalities was 63% and 46% (P = 0.269), whereas EFS was 69% and 51% (P = 0.236), respectively. The OSR and EFS for the cytogenetic abnormalities are shown in Table 1. On comparing the subjects with normal cytogenetics to the other cytogenetic abnormalities, OSR was significantly low for hypodiploidy (P = 0.0362, hazard ratio = 0.4912) and t(9;22) (P = 0.0123, hazard ratio = 0.6327), while other cytogenetic abnormalities did not have a statistically significant difference in OSR [Figure 1]. There was a significant relationship between the two cytogenetic abnormalities, hypodiploidy and t(9;22), with death (P < 0.05). Two patients with t(9;22) received chemotherapy and imatinib at the same time and the remaining patients received only consecutive imatinib. The median duration of treatment was determined as 24 ± 19 standard deviation months. Multivariate logistic regression showed an independent association between the low OSR (P < 0.05) with hypodiploidy and t(9;22), when compared with sex (P = 0.568), age (P = 0.327), median
**Table 1: Frequency of the cytogenetic abnormality in 99 pediatric acute lymphoid leukemia patients**

| Characteristic | Normal | t(12;21) | t(1;19) | t(9;22) | Hyperdiploidy | Hypodiploidy | Miscellaneous |
|---------------|--------|----------|---------|---------|---------------|--------------|--------------|
| n (%)         | 35 (35.3) | 29 (29.3) | 13 (13.3) | 6 (6) | 4 (4) | 2 (2) | 10 (10.1) |
| Sex, n (%)    | 22 (62.8) | 20 (69) | 7 (53.8) | 4 (66.5) | 2 (50) | 2 (100) | 5 (50) |
| Male          | 13 (13.2) | 9 (31) | 6 (46.2) | 2 (33.5) | 2 (50) | 0 | 5 (50) |
| Female        | 21 (60) | 25 (86.2) | 8 (61.5) | 5 (83.4) | 3 (75) | 0 | 6 (60) |
| Lineage, n (%) | 4 (11.5) | 1 (3.4) | 5 (38.5) | 1 (16.6) | 1 (25) | 0 | 3 (30) |
| Pre-B-ALL     | 10 (28.5) | 3 (10.4) | 0 | 0 | 0 | 2 (100) | 1 (10) |
| Common B-ALL  | 1 (3) | 0 | 3 (23) | 0 | 1 (25) | 1 (50) | 1 (10) |
| T-ALL         | 24 (68.5) | 26 (89.7) | 5 (38.5) | 5 (83.4) | 3 (75) | 0 | 5 (50) |
| Median age (years), n (%) | 2 (5.8) | 3 (10.3) | 0 | 2 (33.5) | 0 | 0 | 3 (30) |
| >1            | 33 (94.2) | 26 (89.7) | 4 (66.5) | 7 (70) |
| 1-10          | 9.1 (2.4-13) | 11.3 (5.3-14.9) | 9.8 (4.9-13.5) | 7.8 (2.9-10.8) | 9.8 (4.6-11.3) | 6.6 (2.4-9.8) | 10.2 (5.8-14.7) |
| Median WBC (×10⁶ cells/µl) | 9.3 (0.5-310) | 8.9 (3.2-198) | 7.9 (3.8-208) | 31 (2.3-245) | 11.6 (1.8-174) | 27 (0.8-425) | 10.1 (1.4-370) |
| >50           | 29 (83) | 24 (83) | 9 (69) | 2 (33.4) | 3 (75) | 0 | 6 (60) |
| 50-100        | 3 (8.5) | 3 (10.3) | 3 (23) | 1 (16.6) | 1 (25) | 2 (100) | 3 (30) |
| <100          | 3 (8.5) | 2 (6.7) | 1 (8) | 3 (50) | 0 | 0 | 1 (10) |
| Median PLT (×10⁴ cells/µl) | 52 (10-640) | 67 (25-268) | 59 (15-305) | 38 (20-299) | 49 (34-157) | 20 (16-107) | 41 (26-169) |
| Median peripheral blood blasts (%) | 61 (8-82) | 51 (4-91) | 63 (7-76) | 68 (11-84) | 55 (6-88) | 77 (16-91) | 59 (5-89) |
| Survival outcomes (at 5 year) (%) | 48 | 45 | 41 | 24 | 40 | 23 | 38 |
| OSR           | 39 | 35 | 29 | 24 | 28 | 17 | 25 |
| EFS           | 987 (461-6900) | 801 (357-2661) | 823 (389-1520) | 768 (402-1891) | 545 (380-1123) | 891 (763-979) | 669 (440-3521) |
| Median LDH (IU/l), n (%) | 7 (20) | 19 (56.5) | 8 (61.5) | 2 (33.3) | 3 (75) | 0 | 6 (60) |
| >500          | 25 (71.5) | 7 (24.1) | 3 (23.2) | 3 (50) | 1 (25) | 2 (100) | 2 (20) |
| 500-1000      | 3 (8.5) | 3 (10.4) | 2 (15.3) | 1 (16.7) | 0 | 0 | 2 (20) |

Miscellaneous subgroup comprised patients with mosaic down syndrome, trisomy 21, monosomy 7, inversion 16, and (8;12). ALL: Acute lymphoid leukemia, OSR: Overall survival rate, EFS: Event-free survival, WBCs: White blood cells, PLTs: Platelets, LDH: Lactate dehydrogenase

PLT count (P = 0.431), median WBC count (P = 0.339), MMB (P = 0.782), PBBs (P = 0.561), and lineage (P = 0.420) as potential influencing factors.

On comparing the subjects with normal cytogenetics to the other cytogenetic abnormalities, EFS was significantly low for hypodiploidy (P = 0.0163, hazard ratio = 0.5308) and t(9;22) (P = 0.0131, hazard ratio = 0.4908), while other cytogenetic abnormalities did not have a statistically significant difference in EFS [Figure 2]. Multivariate logistic regression showed an independent association between the low EFS (P < 0.05) with hypodiploidy and t(9;22), when compared with sex (P = 0.657), age (P = 0.438), median PLT count (P = 0.985), median WBC count (P = 0.769), MMB (P = 0.599), PBBs (P = 0.999), and lineage (P = 0.809) as potential influencing factors.

**Discussion**

The current study included 221 pediatric ALL patients, of which 99 (44.8%) had assessable cytogenetic abnormalities. This was almost similar to that seen in a study by Fletcher et al. (45.2%) but lower than that observed in a study by Ghaffari, et al. (52%) and Pullarkat et al. (65.5%).

In studies by Pandita et al., Settin et al., and Chennamaneni et al., the median age of ALL patients was 7.4, 7.7, and 13 years, respectively, whereas it was lower in our study (6.3 years, range: 6 months to 14 years).

In this study, there was a higher frequency of the ALL in boys with a male: female ratio of 1.67:1 which was similar to the study by Settin et al. (male:female ratio: 1.73:1) and Chennamaneni et al. (male:female ratio: 2.57:1), but this was different in the study by Pandita et al. so that girls had a higher frequency (male:female ratio: 0.8:1).

In the present study, the frequency of B-ALL was higher than that of T-ALL, so that 83% of patients had BALL and 16% had TALL. In studies by Forestier et al., Chennamaneni et al., and Chessels et al., the frequency of B-ALL and T-ALL was 93.2% and 6.8%, 68% and 31%, and 79.5% and 8.6%, respectively, which was consistent with our findings. The results indicate a high prevalence of TALL which can be due to underlying factors and the prevalence of viral infections.

Of the 99 patients with assessable cytogenetic abnormalities, 35.3% of patients had normal cytogenetic, 29.3% had t(12;21), t(8;12), t(9;22), t(1;19), and t(12;21) so that 83% of patients had BALL and 16% had TALL, which was consistent with our findings.
13.3% had t(1;19), 6% had t(9;22), 4% had hyperdiploidy, 2% had hypodiploidy, and 10.1% had miscellaneous cytogenetics. Compared to the other studies by Pandita et al., Chessels et al., Chennamaneni et al., and Forestier et al., the percentage of t(12;21) and t(1;19) was higher in our study, while the incidence of hyperdiploidy was lower in our study. A higher percentage of normal cytogenetic was observed in our study than the study by Pandita et al. but this was higher in the study by Chennamaneni et al. than our study. Compared to the studies by Forestier et al. and Chessels et al., the percentage of t(9;22) was higher in our study, but this was higher in the study by Chennamaneni et al. and Pandita et al. than our study.

In this study, hypodiploidy and hyperdiploidy were found in 2% and 4% of patients, respectively. Seventy-five percent of hyperdiploidy was seen in the pre-B-ALL subgroup and 25% in common B-ALL. However, total hypodiploidy was seen in the T-ALL subgroup. In parallel with our study, in a study about the cytogenetic characteristics of Chinese patients with ALL, the authors found that 4.9% of children showed hypodiploidy. Furthermore, Silva et al. reported hyperdiploidy and hypodiploidy in 38.5% and 6.6% of the children ALL patients, respectively. The most common cytogenetic abnormality found in pediatric ALL is reported to be t(12;21). The frequency of t(12;21) in this study was 29.3%, which was the most common cytogenetic disorder after patients with normal cytogenetic. In Fars Province, Safaei et al. reported that the frequency of hyperdiploidy was the most common (32%) cytogenetic abnormality and the frequency of

Figure 1: Estimated overall survival rate of all enrolled patients based on cytogenetic abnormality. Kaplan–Meier estimate for OSR of (a) the six cytogenetic abnormalities, (b) normal cytogenetic versus t(1;19), (c) normal cytogenetic versus t(12;21), (d) normal cytogenetic versus t(9;22), (e) normal cytogenetic versus hyperdiploidy, (f) normal cytogenetic versus hypodiploidy, and (g) normal cytogenetic versus miscellaneous.
t(9;22), hypodiploidy, and t(1;19) was 11%, 7.69%, and 5%, respectively,[28] which was almost similar to our study.

The normal cytogenetic group had a higher median LDH compared to other cytogenetic abnormalities. In a study by Chennamaneni et al., the median LDH was higher in the miscellaneous group.[18] The median WBC count and PBBs were higher in the subgroups with t(9;22) (31 × 10^9/µl) and hypodiploidy (27 × 10^9/µl), while median Hb and PLT count

Figure 2: Estimated event-free survival of all enrolled patients based on cytogenetic abnormality. Kaplan–Meier estimate for event-free survival of (a) the six cytogenetic abnormalities, (b) normal cytogenetic versus t(12;21), (c) normal cytogenetic versus t(1;19), (d) normal cytogenetic versus t(9;22), (e) normal cytogenetic versus hyperdiploidy, (f) normal cytogenetic versus hypodiploidy, and (g) normal cytogenetic versus miscellaneous
were lower in these subgroups. In a study by Chennamaneni et al.,[18] the median WBC count was higher in t(9;22) and hypodiploidy subgroups, and the median Hb was higher in the subgroup with t(12;21), t(1;19), and hyperdiploidy which were consistent with our findings. A similar percentage of PBBs was also seen in the study by Chennamaneni et al.[18]

In our study for all cytogenetic abnormalities, the 5-year OSR and EFS were 48% and 43%, respectively, but compared to various studies by Chennamaneni et al., Radhakrishnan et al., Hunger et al., C Shanta et al., Hessells et al., and Pui et al., OSR ranged from 37% to 94% and EFS ranged from 28% to 85.6%.[18,29‑33]

The 5-year OSR for B‑ALL and T‑ALL abnormalities were not statistically similar. Different results were also reported in the study by Chennamaneni et al. (3-year OSR and EFS: P < 0.05) and Goldberg et al. (5-year OSR and EFS: P < 0.05). [18,34]

In the present study, the OSR and EFS were significantly low for the hypodiploidy and t(9;22), while other cytogenetic abnormalities did not have a statistically significant difference compared to cytogenetic abnormalities. In several studies, the 5-year EFS for t(9;22) patients ranged from 9% to 25%.[18,35] which was consistent with our findings.

**Conclusions**

Our results emphasized the importance of the cytogenetic findings in evaluating the survival outcomes, which allows identifying a variety of OSR and EFS, because some of the cytogenetic abnormalities may interfere with the death and prognosis.

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**Conflicts of interest**

There are no conflicts of interest.

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