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Molecular and cytogenetic evaluation of pediatric leukemias

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Abstract

Objective: This study was conducted to determine the rate of genetic changes that may be a risk factor in the treatment of our leukemia patients.

Method The study was conducted prospectively in 39 patients who were followed in department of pediatric hematology. Bone marrow or peripheral blood samples (with more than 30% blast invasion) evaluated for cytogenetics before the leukemia treatment. TEL/AML1 probe was applied to 18 of 20 acute lymphoblastic leukemia (ALL) patients and mixed lineage leukemia (MLL) probe was applied to 3 patients with infantile leukemia diagnosis.

Results: Chromosomal aberration was detected in 8(40%) of 20 patients with ALL diagnosis and in 6(60%) of 10 patients with acute myeloid leukemia (AML) diagnosis. Translocation involving the MLL gene region was detected cytogenetically in two of three patients with infantile leukemia while in the other patient, it was shown by Fluorescence In Situ Hybridization analysis. TEL/AML1 fusion was detected in 5(27.7%) of 18 patients with a diagnosis of B-precursor ALL. Amplification of the AML1 gene was defined in 7(38.8%) of 18 pediatric ALL patients.

Conclusion: Cytogenetic investigations should be continued in leukemia patients. The rate of chromosomal aberrations in ALL and AML patients was consistent with the literature. The rate of TEL/AML1 gene fusion which is a good prognostic factor in ALL patients, was consistent with the literature.

Keywords: Leukemia, cytogenetic analysis, prognosis

INTRODUCTION

Leukemia is the most common malignancy worldwide in children and is caused by the proliferation of hematopoietic cells that lead to impaired normal bone marrow function and bone marrow failure. Leukemias account for 27% of childhood cancers in the United States (1).

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for a quarter of all childhood cancers and three-quarters of all newly diagnosed acute leukemia patients. ALL is divided into B-cell and T-cell ALL subgroups. ALL is most common between the ages of 1 and 4. T-cell ALL is more common in males and in adolescents (2). Although the etiology of ALL is unknown in most of the cases, various genetic syndromes such as Down syndrome have been associated with an increased risk of leukemia (3). The survival rate in ALL patients reached 85.9% with multidisciplinary approaches (4).

Acute myeloid leukemia (AML) accounts for approximately 15-20% of leukemias in children. It can occur at any age, but its frequency is higher in adolescence. Although the results have improved in the last 10 years in AML patients, survival is around 70% (5). In chronic myeloid leukemia (CML), leukemia cells have not lost their ability to differentiate.

In childhood leukemias, age, leukocyte count, immunophenotyping, and “karyotyping” have an important diagnostic and prognostic value. Molecular analysis of chromosomal numerical or structural irregularities is also important in understanding the biology of the disease and elucidating the roles of these irregularities in leukomogenesis.

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Determination of these specific chromosomal abnormalities at the time of diagnosis and after treatment useful monitoring the disease, evaluating the response to therapeutic drugs, and monitoring minimal residual disease (6).

The aim of this study is to reveal chromosomal changes and chromosome rearrangement in leukemia patients.

METHOD

Patients

A total of 39 patients, 20 ALL, 10 AML, 8 mixed-lineage leukemia (MLL) and 1 CML patients, who were admitted to the Department of Pediatric Hematology at Ondokuz Mayıs University between 2005 and 2007, were included in the study. In the initial diagnosis, morphological examination of bone marrow, flow cytometry and genetic analyzes were performed. ALL BFM 2002 protocol, AML BFM 2004 protocol and AML or ALL protocol were applied according to the type of mixed leukemias.

The study protocol was accepted by Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (Decision No: 2005/354) and informed consent was provided by the parents of the patients before the study.

Patients' demographic features such as age, gender, blood count at the time of diagnosis, blast rate in the bone marrow and peripheral blood and immunophenotyping results were recorded. Cytogenetics and Fluorescence In Situ Hybridization (FISH) technics were applied to bone marrow or peripheral blood samples (with more than 30% blast invasion) before the leukemia treatment. The identification of chromosomes in the study was made according to the "International System For Human Cytogenetic Nomenclature (ISCN) 2005" (7). Structural ≥2 and numerical ≥3 chromosomal aberration detection was considered clonal.

Cytogenetic and FISH Method

Karyotype analysis was carried out on lymphocyte culture of all patients using the conventional method. According to the standard protocols, four well spread G-banded metaphases were karyotyped and at least 20 metaphases were examined with a 450 bands resolution for each patient. FISH analysis with probes (Vysis Inc., Downer's Grove, IL, U.S.A) were performed on both metaphase spreads and interphase nuclei according to the guideline of manufacturer. Image analyses were evaluated using CytoVision software (version 3.93; Applied Imaging) with Olympus BX51 microscope equipped with Progressive Scan Video Camera. During the FISH analysis, at least 200 cells were counted from each patient slide. The positivity threshold value was taken as 3% for each probe. Positivities above this value were considered significant.

Identification of the probe

TEL/AML1 probe:

A normal nucleus hybridized with "LSI TEL/AML1 ES Dual Color Translocation Probe" (Vysis Inc., Downer's Grove, IL, U.S.A.) shows 2 red and 2 green signals. It is expected in a nucleus containing TEL/AML1 fusion that a green (TEL), a large red (AML1), a small red (residual red) and a yellow signal appear.

MLL Probe: With the "LSI MLL Break Apart Rearrangement Probe" (Vysis Inc., Downer's Grove, IL, U.S.A) used in FISH analysis, two red/green (yellow) fusion signal patterns are seen in the absence of MLL gene rearrangement in the cell. In the presence of MLL translocation, a red/green (yellow) fusion signal, a red signal and a green signal are expected.

Statistical Analysis

SPSS v21 IBM Corp, NY, USA software was used to analyze the data. First, distributed demographic characteristics (eg, age and gender) and clinical member descriptive statistics were evaluated. In this evaluation, frequencies and percentages were calculated for the data belonging to the categories. Since the number of patients was <30 in the study, non-parametric tests were preferred. Normal distribution data were expressed as median and interquartile range (IQR). Kruskal Wallis Test was used to compare numerical data between three independent groups, and Mann Whitney U test was used to compare subgroups. Chi-square test was used to compare categorical data. "In the analyses, a significance level of $p<0.05$ was considered statistically significant.

RESULTS

The study included 39 patients, 21 (53.8%) of were girls. The median age at admission was 56.5 months (IQR=60.5) in the ALL patient, 143.5 months (IQR=45) in the AML patient, 48 months (IQR= 53) in the mixed leukemia patient, and 155 months in the KML patient. The median leukocyte count was 24.7 $x10^9$ (IQR=83.6 $x10^9$) in the ALL patient, 11.2 $x10^9$ (IQR=11.9 $x10^9$) in the AML patient, 8.1 $x10^9$ (IQR=75.6 $x10^9$) in the mixed leukemia patient, and 171.0 $x10^9$ in the KML patient (Table 1). A significant relationship was detected between leukemia types and age at diagnosis with the Kruskal Wallis Test ($p=0.002$, $p<0.05$). A significant relationship was found between mixed and AML, and between AML and ALL by Mann Whitney U test ($p=0.013$, $p=0.003$, respectively). No significant relationship was detected between leukemia types and sex and leukocyte count with the Kruskal Wallis Test.

Chromosomal aberration was detected in 8 (40%) of 20 patients with ALL diagnosis by cytogenetic analysis. Aberration was detected in 6 (60%) of 10 patients with AML diagnosis and in 4 (50%) of 8 patients with mixed leukemia (Tables 2, 3 and 4). Metaphase was not detected in 1 patient each in the ALL, AML and mixed leukemia groups.

Table 1. Baseline patient characteristics

Immunphenotype	Number	Age in month Median (IQR)	Leukocyte count/L Median (IQR)	Follow-up time Median (IQR)
ALL	20	56.5 (60.5)	24.7 x10^9 (83.6 x10^9)	13 (7)
AML	10	143.5 (45)	11.2 x10^9 (11.9 x10^9)	12.5 (14)
MLL	8	48 (53)	8.1 x10^9 (75.6 x10^9)	9.5 (7.5)
CML	1	155	171.0 x10^9	7

Abbreviations: IQR, interquartile range; ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; MLL, mixed-lineage leukemia CML, Chronic myeloid leukemia

MLL rearrangement probe was applied to 3 patients diagnosed with infantil leukemia. In 2 had B-precursor leukemia and 1 mixed type leukemia patients was detected. In one of the infantile leukemia patients MLL gene rearrangement was revealed by FISH analysis (Table 5).

TEL/AML1 probe was applied to 18 of 20 ALL patients. TEL/AML1 fusion positivity was detected in 5 of 18 (27.7%) patients with B-precursor ALL. Amplification of the AML1 gene was defined in 7 of 18 (38.8%) pediatric ALL patients. One patient with B-precursor immunophenotype had a TEL/AML1 gene fusion and TEL gene deletion (Table 2).

DISCUSSION

Leukemia is a common disease in recent years. In leukemia treatment, treatment schemes are selected according to risk classification. Chromosome and genetic research are the main elements of risk classification, especially in ALL and AML. In CML, diagnosis must be made based on genetic mutations. In some leukemia translocations and mutations, mutation-specific drugs have been discovered and put into routine use. In order for these drugs to be used in the patient, this mutation must be detected in molecular studies.

The use of mutation-specific drugs (For example: tyrosine kinase inhibitors in CML) changes the prognosis of patients.

Table 2. Results of cytogenetic and TEL/AML1 fluorescence in situ hybridization (FISH) analysis of acute lymphoblastic leukemia diagnosed patients

Karyotype	Number	Percentages (%)
Normal	11	55.0
High hyperdiploidy (51-67 chromosomes)	4	20
t(4;11)(q21;q23)	1	5
t(7;10)(q11;p11)	1	5
del(6)(q21q25)	1	5
inv(9)(p11;q12)	1	5
No metaphase	1	5
FISH	**Number**	**Percentages (%)**
TEL/AML1fusion	5	27.7
TEL/AML1 fusion and TEL deletion	1	5.5
AML1(>3copies gene)	7	38.8

Many mutation-specific drugs have been produced for other leukemias or phase studies are ongoing. For this reason, the importance of performing molecular genetic studies on patients is increasing. In this study, the genetic findings of patients treated at our university were examined. By examining these findings, it was investigated whether there were regional differences.

Although ALL is generally seen in previously healthy individuals, environmental risk factors and inherited genetic predisposition are thought to have an impact (8). Although approximately 80% of patients recover, some patients develop resistance to treatment and this worsens the prognosis in patients (9).

While 49.2% of chromosomal aberrations can be identified with the G-banding technique, 73.8% of the gene arrangements have been identified with the use of FISH analysis (10). Accordance with the literature, in this study, the frequency of chromosomal aberration was found in 8 (40%) of 20 ALL patients with cytogenetic results. When FISH analysis was added, it was observed that 55.5% of the gene arrangements were identified.

In a study of large series in which 371 AML patients were included, the rate of chromosomal aberration in AML was found to be 68-85% (11-13). In this study, the rate of chromosomal aberration in patients with AML was found to be 60.0%, consistent with the literature. All these differences are thought to be related to the methodological approaches used, especially the FISH method is believed to allow a higher rate of detection of cryptic changes. It is also conceivable that the differences may be due to geographical distribution and

racial genetic factors.

Recurrent chromosomal abnormalities such as t(12;21), t(9;22), 11q23 rearrangement, hypodiploidy, trisomy/polysomy 21 and der(21)t(21;21) duplication are observed in childhood ALL patients. Among these abnormalities, t (12;21) translocation, which is the most common abnormality among childhood ALL cases, is a good prognostic marker for the course of the disease (10,14). Translocation t (12;21) (p13;q22) resulting in the TEL-AML1 fusion gene is a chromosomal abnormality with a frequency of approximately 25% in childhood ALL patients (15). The non-translocated TEL allele t (12;21) is deleted in approximately 70% of ALL patients, and this subtype also has a good prognosis (16,17).

Table 3. Results of cytogenetic analysis of acute myeloid leukemia diagnosed patients

Karyotype	Number	Percentages (%)
Normal	3	30
Low hyperdiploidy (47-50 chromosome)	2	20
Hypodiploidy (<44 chromosome)	2	20
t(7;14)(p15;q32)	1	10
t(8;21)(q22;q22)	1	10
No metaphase	1	10

Table 4. Results of cytogenetic analysis of mixed leukemia and chronic myeloid leukemia

Mixed leukemia karyotype	Number	Percentages (%)
Normal	3	37.5
Low Hyperdiploidy (47-50 chromosome)	1	12.5
t(1;11)(p32;q23)	1	12.5
t(9;22)(q34;q11)	1	12.5
del(12)(p11p13)	1	12.5
No metaphase		12.5
Chronic myeloid leukemia karyotype	**Number**	**Percentages (%)**
t(9;22)(q34;q11)	1	100

Since the t(12;21) translocation is virtually undetectable by conventional cytogenetic procedures, the FISH method was used. In the study, TEL/AML1 fusion was detected with an incidence of 27.7% (5/18) in B precursor ALL patients. The frequency of TEL/AML1 fusion is in Scandinavian countries (25%) (18), USA (22%) (19) and India (7%) (20). It can be thought that frequency differences may be due to geographical distribution and racial genetic factors.

The incidence of additional abnormalities in TEL and AML1 genes in t (12; 21) positive ALL patients was determined as 20%. Previous studies have reported inconsistent results regarding the prognostic effects of additional genetic changes. Attarbaschi et al.(21) reported that in patients with TEL /AML1 fusion, TEL deletions, trisomy 21 and additional der (21) t (12;21) were detected with 55%, 14% and 15%, respectively, and also reported that the presence of TEL deletion in TEL/AML1 positive patients has a worse prognosis than those without.

In different study, TEL deletions in TEL/AML1 positive pediatric ALL patients are associated with better prognosis (22). For example, it was reported that there was no significant difference in clinical features and results according to the presence or absence of additional genetic changes (23).

It detected TEL deletion with TEL/AML1 fusion in 1 of the 18 B precursor ALL patients using TEL/AML1 probe. The patient remained in remission for 16 months.

Table 5. Results of FISH analysis performed with LSI MLL dual color, break apart rearrangement probe, relapse status and survival months of the infantil leukemia diagnosed patients

Age (in month)/ Sex	Leukemia type	Karyotype	MLL TR	Relapse (months)	Survival (months)
3.5 /Female	B-precursor	46,XX,t(4;11)(q21;q23)	+	NR	2 (death)
2/Female	B-precursor	46,XX	+	NR	2 (death)
6/Female	Mixed	46,XX,t(1;11)(p32;q23)	–	8	8

It detected three TEL/AML1 fusions in a patient with a cytogenetically normal karyotype. No relapse was observed in the patient during the 21-month follow-up.

In the literature, the rate of detecting three or more copies of the RUNX1 gene on chromosome 21 without polysomy was 21.4% (24). In this study, amplification of the AML1 gene was defined in 7 of 18 (38.8%) pediatric ALL patients. AML1 amplification was not observed in fusion carriers. Of these, 4 patients had three or more copies of the AML1 gene without chromosome 21 polysomy. Six AML1 copies were detected in 1 patient. He was in remission during the 15-month follow-up.

In this study, high hyperdiploid karyotype was detected in 2 of 19 patients (10.5%) with ALL diagnosis. High hyperdiploid karyotypes (chromosome number between 51-67) are numerical anomalies frequently (30%) seen in childhood B-cell ALL and are considered good prognosis markers. Trisomies and tetrazomies of 4,6,10,14,17,18, 21 and X chromosomes are frequently seen in hyperdiploid karyotypes (25). Similary, in this study, the most common chromosome gain was observed on 14, 20, 21 and X chromosomes. In hyperdiploid karyotype, it has been reported that especially trisomy 4 and trisomy 10 association is an indicator of low

relapse and better prognosis (26).

Combination of trisomy 4 and trisomy 10 was detected in 1 patient. It was observed that this patient remained in remission during the 23-month follow-up period.

KMT2A gene which was formerly known as the MLL gene is observed in 5% of child with ALL. However, when leukemia develops in infants, the frequency of KMT2A rearrangements increases to 70-80% (27).

Due to the term 'mixed' gene, MLL is rearranged with more than 80 different most frequently observed AF4, AF9, ELL, and ENL partner genes and have been shown to result in translocations (4; 11) (q21;q23), t (9; 11)(q22;q23), t (11;19) (q23; p13.1) and t (11;19) (q23; p13.3) respectively (28). The prognosis in infant ALL children with the 11q23 rearrangement is worse than in those without this rearrangement (29).

In this study, in 3 patients with infantile leukemia was detected the KMT2A rearrangement by cytogenetic and FISH analysis. A 3.5-month-old patient with B-precursor ALL presented with high leukocyte count (199 x10^9/L) and t(4;11) (q21;q23) was detected in peripheral blood cytogenetic examination. Infantile ALL induction therapy was initiated for the patient. Due to the development of sepsis during the course of the treatment, chemotherapy could not be completed and the patient died two months after the diagnosis. In a 6-month-old infantile leukemia patient with mixed immunophenotype, t(1;11)(p32;q23) was detected in bone marrow cytogenetic analysis. This translocations were not common translocations. Patient with t(1;11)(p32;q23) translocation developed a relapse eight months after relapsed despite intensive treatment.

Molecular cytogenetic techniques such as FISH are particularly valuable in patients where analyzable metaphase cells cannot be obtained or standard cytogenetic analysis cannot be performed in the presence of only a few low-quality cells. They are also required for cytogenetically identifying cryptic abnormalities

CONCLUSION

The genetic results found in this study contributed to the risk stratification of our patients. Molecular results were found in CML in the molecular therapies group. The rate of chromosomal aberrations in ALL and AML patients was consistent with the literature. TEL/AML1 gene fusion rate, which is a good prognostic factor in ALL patients, was consistent with the literature.

Limitations of the study

This study has limitations such as being a single-center with a limited sample size. Multicenter, prospective studies with larger sample sizes and longer follow-up times should be planned to validate the results.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Thesis

This study was prepared by rearrangement of the specialty thesis by 2008, entitled as "Chromosome analyzes and fluorescent in situ hybridization studies in childhood leukemias".

Ethical Declaration

Ethical permission was obtained from the Ondokuz Mayıs University, Medical Faculty Clinical Research Ethics Committee for this study with date 12.28.2005 and number 354, and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions

Concept: MA, UA, Design: MA, UA, Supervising: UA, DA, Financing and equipment: MA, UA, DA, Data collection and entry: MA, Analysis and interpretation: MA, UA, DA, Literature search: MA, Writing: MA, Critical review: UA, DA

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