Original Article

11q23 Translocation in Children with Acute Lymphocytic Leukemia Following Primary Response to Chemotherapy: Prognostic Significance and Diagnostic Accuracy

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Abstract

Background: Cytogenetic abnormalities in leukemia cells have strong prognostic values for different clinical subgroups, clinical features, and therapeutic outcomes. **Patients and Methods:** This study was conducted on 100 children with acute lymphocytic leukemia referred to Ahvaz Shafa Hospital during 2012–2017. The patients were diagnosed by a specialist through examination of morphology and flow cytometry, testing bone marrow specimen on the 7th day of treatment, and a karyotype and cytogenetic test are performed. **Results:** There was no relationship between the t(11q23) and gender nor age of children. Besides, the mean white blood cell (WBC) counts in patients who were negative for 11q23 and those positive revealed a statistically significant relationship between WBC count and 11q23 ($P = 0.022$). **Conclusion:** A significant association between the 11q23 translocation and primary response to chemotherapy is existed. Diagnostic accuracy of these tests for detecting t(11q23) is generally high, as well as sensitivity and specificity are optimal for all anomalies.

Keywords: *11q23 translocation, acute lymphoblastic leukemia, cytogenetic, diagnostic accuracy, prognosis*

Introduction

Acute lymphocytic leukemia (ALL) is one of the most common types of childhood cancer that affects different types of lymphocytes (B-cells or T-cells) that make up lymphoid tissues and develops and gets worse quickly.[1] ALL accounts for approximately 75% of childhood leukemia.[2] ALL is divided into subtypes based on the type of involved lymphocytes and the B-cell subtype counts for 80%–85% of all ALL types, compared with the 15% share of the T-cell subtype of children and adults.[3] The etiologies of the disease are not fully known, but the current evidence a multifactorial etiology for ALL including genetic and environmental factors.[4] A number of clinical and laboratory parameters have prognostic value in ALL children, which can play significant role in designing treatment and management of the disease.[5] These factors include the age of patient at the time of diagnosis, white blood cell (WBC) count, gender, platelet count, hemoglobin level, serum immunoglobulin level, race, response to treatment, blast cell morphology, and a number of chromosomal abnormalities, especially translocations.[6]

Chromosomal translocations or displacements are abnormalities, caused mainly by chromosomal defects and are one of the most important risk factors of cancers.[7] The most common translocation in ALL is t(12; 21), which is associated with a favorable prognosis that usually occurs in 1–10 years old children.[8,9] Children younger than 5 years of age often exhibit chromosomal abnormalities of type t(4; 11) translocation, with a high risk of failed therapies. Philadelphia chromosome t(9; 22) accounts for about 5% of entire ALL patient but does not have high prognostic value for the disease.[10] Chromosome 11 translocations are the most common chromosomal abnormalities in ALL.[11] These translocations are present in approximately 15% of ALL cases, 5% of acute myeloid leukemia (AML) cases, and 85% of secondary leukemia associated with anticancer agents of topoisomerase II inhibitors.[12,13]

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Cytogenetic analysis is one of the most important diagnostic tools for determining the prognosis in hematologic malignancies, particularly ALL. Therefore, the diagnosis of chromosomal abnormalities, including deletion, duplication, and inversion, has strong prognostic value in choosing appropriate treatment, recovery strategy, and clinical approach to these patients.[14,15] Furthermore, genetic diagnosis in these patients is an important factor in genetic counseling that could predict the risk of subsequent offspring with greater accuracy.[16]

The present study was aimed to investigate the prognostic value and diagnostic accuracy of 11q23 translocation and its relationship with other prognostic factors such as age, sex, and therapeutic response in childhood ALL.

Patients and Methods

Study design

This prospective study was conducted on 100 children with ALL who were referred to Ahvaz Shafa Hospital, Ahvaz, Iran during 2012–2017. This study was approved by the local ethics committee of Ahvaz Jundishapur University of Medical Sciences, which were in complete accordance with the ethical standards and regulations of human studies of the Helsinki declaration (2014). Before the enrollment, the experimental procedures, objectives, possible benefits, and adverse effects of the study were clearly explained to all participants, and then all participants filled and signed a written consent form for their participation in the study.

Participants

Children diagnosed with ALL, according to morphologic and flow cytometric findings, are provided by a specialist physician specializing in bone marrow testing and are introduced for karyotyping and cytogenetic testing, were enrolled. Besides, the bone marrow sample is obtained on the 7th day of the chemotherapy and bone marrow samples (amount to 5 ml) were collected using a heparinized complete blood count (CBC) glass. Then, the collected samples were sent to the laboratory for karyotype and cytogenetic testing.

Methods

Preparation of chromosomes is performed by peripheral blood culture with phytohemagglutinin mitogen or by bone marrow culture on lam, which was the same as the karyotyping technique in the patients. The obtained chromosomes were then stained with Giemsa color and then denatured with trypsin. Then, at the end of the first step, mitotic analysis was performed to detect various numerical and structural chromosome abnormalities. In the second step, these chromosomes were combined with the probe in a humidified incubator for 10 min and at a temperature of 80°C–75°C to be denatured. Then, after washing, the probe and the chromosome were brushed. In the final step, a special fluorescence color the staining was used and depending on the selected color; the background was stained with a color and chromosome in the opposite color. The fluorescence *in situ* hybridization (FISH) technique was applied to slides that were not stained and analyzed by cytogenetics.

Statistical analysis

In this study, descriptive indexes, such as mean, interquartile, range, and standard deviation, were used to describe the quantitative variables (age and WBC). Frequency and frequency were used to describe the qualitative variable such as gender. Normality of quantitative variables was evaluated using Shapiro–Wilk test. Single-variable analysis was used to examine the relationship between quantitative and gender variables with cytogenetic status using Mann–Whitney nonparametric test (in cases of nonnormality of the quantitative variables assessed by Mann–Whitney test) and Chi-square test. In addition, multivariate analysis of data was performed using logistic regression model. To evaluate the molecular testing diagnostic function in distinguishing between negative and positive 11q23 translocation of diagnostic measures such as sensitivity, specificity, positive, and negative predictive value, accuracy, Youden's Index, positive and negative likelihood ratio, and area under the receiver operating characteristic (ROC) curve (area under the curve [AUC]) area under the ROC curve. In this study, the statistical analyses were performed with R programming (version 3.03). In all statistical analyzes, the significance level was set at 0.05.

Results

From 100 children with ALL, 86 cases (86%) were pre-B-lineage and 14 cases (14%) were T-lineage subtype [Table 1]. t(9, 22) breakpoint cluster region-Abelson murine leukemia (p190) (6%) was the most frequent cytogenetic abnormalities in patients with ALL [Table 1].

Molecular and cytogenetic findings in patients with ALL are presented in details [Table 2]. Using FISH on 31 patients were positive in terms of the 11q23 translocation [Table 2]. There was no relationship between the 11q23 translocation and gender [Table 3]. Results showed no difference between the age of children and positive or negative 11q23 translocation (P = 0.6). Moreover, the mean WBC counts in the patients who were negative or positive for 11q23 translocation revealed a statistically significant relationship between WBC count and 11q23 translocation (P = 0.022).

The diagnostic accuracy of clinical parameters and a positive 11q23 translocation could verify the clinical suspicion of ALL. In this regard, molecular findings increased the prediction sensitivity of the 11q23 translocation to 90% (95% confidence interval [CI] = 74%–98%, [Table 3]).

The corresponding ROC curve for molecular findings compared with cytogenetic analysis is presented in Figure 1. As expected, the diagnostic accuracy for 11q23

Table 1: Demographic features of patients with acute lymphocytic leukemia (*n*=100)

Characteristic	Values
Age (year), mean±SD	5.67±3.70
Gender, *n* (%)	
Male	38 (38)
Female	62 (62)
WBC count (×10^9/L), mean±SD	17.41±21.6
Lineage, *n* (%)	
Pre-B	86 (86)
T	14 (14)
Cytogenetic, *n* (%)	
46xy	61 (61)
46xx	9 (9)
46xy, t(9,22)	6 (6)
46xy, t(12,21)	5 (5)
46xx, t(4,11)	4 (4)
46xy, t(9,22)	2 (2)
Other (46xx, inv16; 46xx, t(11;19), del5p; 46xx, t(2,8), t(4,11); 46xy, t(1,19); 46xy, del2; 46xy, der(3); 46xy, t(1,11) ; 46xy, t(1,11), t(4.11); 46xy, t(1,14); 46xy, t(1;11) del15; 46xy, t(11;19), del18; 46xy, t(4,3); 46xy.t(9,11),(14,22))	Each one 1 (1)

SD: Standard deviation, WBC: White blood cell

Table 2: Molecular and cytogenetic findings in patients with acute lymphocytic leukemia

Baseline characteristic	Patients (*n*=100)	*P*
All patient (*n*)/total, *n* (%)		
Negative	69/100 (69)	<0.01
Positive	31/100 (31)	
Age (year), mean±SD		0.6
Negative	5.84±3.86	
Positive	5.3±3.41	
Gender (*n*)/total, *n* (%)		
Male		
Negative	25/69 (36.24)	0.504
Positive	13/31 (41.9)	
Female		
Negative	44/69 (63.76)	0.546
Positive	18/31 (58.1)	
WBC count (×10^9/L), mean±SD		
Negative	17.86±20.56	0.022
Positive	16.41±24.70	

SD: Standard deviation, WBC: White blood cell

translocation detection with functional significance by molecular findings, compared with the cytogenetic data as the reference, was 84.9% [Figure 1; AUC = 0.849, 95% CI: 0.776–0.921].

Discussion

ALL is a common disease in children that is associated with various pathogenesis. The occurrence of mutations and genetic translocations are one of the main pathogenic causes of the disease.[17,18] Recent studies have shown that the occurrence of translocations in ALL patients in response to therapeutic agents is important in responding to patient treatment and controlling the progression of the disease.[17] On this basis, it has been shown that some of the translocations such as t(12; 21) that produce the ETV-RUNX-1 fusion are accompanied by strong prognosis, while 11q23 translocation is with poor prognosis and associated with disease progression.[19] The findings of the present study showed that integrating functional data including cytogenetic assessment, from diverse modalities increases diagnostic accuracy**.** The present study reported a significant association between 11q23 translocation and absence of preliminary response to chemotherapy and WBC counts; however, the associations between 11q23 translocation and other variables such as gender and age, were not statistically significant, which could be attributed to the small sample size of this study.

Motlló *et al*. investigated the relationship between 11q23 translocation and its prognostic value in ALL patients. They reported no relationship between the 11q23 translocation with age, sex, and WBC of the patients.[20] Moreover, Pigneux *et al*. showed that AML patients with 11q23 translocation did not show complete treatment response and thus disease improvement. They concluded that bone marrow transplantation is necessary in these patients.[21] In addition, a study by Zuo *et al*. reported that patients with myelodysplastic syndrome with 11q23 translocation were resistant to treatment and showed disease recurrence, and the disease progression to AML was accelerated.[22] Basically, gender does not play a crucial role at AML incidence, particularly among the children.[23] Former studies on the role of age in AML incidence, have reported that increasing age was associated with elevated AML incidence, particularly during infancy.[24] A synthetic analysis of large population on several trials on the diagnostic

Table 3: Sensitivity, specificity, false positive and negative rate, positive and negative predictive values, accuracy, Youden's Index, positive and negative likelihood ratio of molecular and cytogenetic findings in prediction of the 11q23 translocation and their 95% exact confidence interval

Measures of diagnostic accuracy	Value (%)	95% CI
Sensitivity	90	73.47-97.89
Specificity	79.71	68.31-88.44
False-positive rate	20.29	68.31-88.44
False-negative rate	10	2.11-26.53
Positive predictive values	65.85	49.41-79.92
Negative predictive values	94.83	85.62-98.92
Accuracy	82.83	73.94-89.67
Youden's Index	69.71	41.78-86.33
Positive likelihood ratio	4.44	2.74-7.19
Negative likelihood ratio	0.13	0.04-0.37

CI: Confidence interval

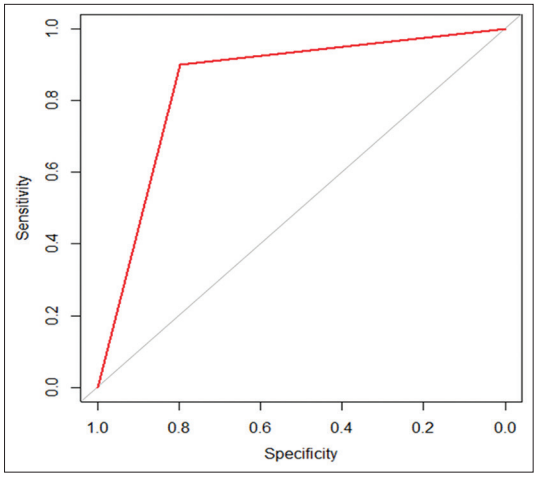

Figure 1: Area under the receiver operating characteristic curve of molecular findings in prediction of 11q23 translocation compared with cytogenetic data as reference with 95% confidence interval

value of cytogenetic abnormalities on treatment outcome in leukemia, provided the framework for stratifying treatment method of the disease, which has been adopted in the recent trials.[25] A large series of consecutive analyses on patients with leukemia using FISH and multiplex-FISH (M-FISH) techniques reported the sensitivity of conventional cytogenetic methods as 73%, compared with FISH. In conclusion, the authors recommended cytogenetic analysis be complemented by molecular or FISH methods to unravel leukemia rearrangements.[26] Another retrospective study with large sample size of children with leukemia revealed that diagnostic accuracy of cytogenetic approach combined with molecular techniques for detecting 11q23 translocation is generally high, whereas the sensitivity is not optimal for all anomalies.[27] In agreement with these findings, our study reported accuracy of about 85% for combined molecular and cytogenetic methods.

Conclusion

Leukemia rearrangements could be associated with poor outcome in pediatric patients with ALL. Moreover, a significant association between 11q23 translocation and primary response to chemotherapy exists, but no correlation was observed between this translocation with age or gender of the patients. Therefore, conducting further studies using molecular and cytogenetic tests are necessary to support these findings. Diagnostic accuracy of these tests for detecting 11q23 translocation is generally high and also sensitivity and specificity are optimal for all anomalies.

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Conflicts of interest

There are no conflicts of interest.

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