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Detection Of 11q23 Gene Rearrangement In Children With Acute Lymphoblastic Leukemia And Its Association With Demographic Data and Response To Initial Chemotherapy On The Seventh Day Of Induction

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer leading to cancer-related death in children. Most infants with ALL harbor recurring structural chromosomal rearrangements that are important initiating events in leukemogenesis but are insufficient to explain the biology and heterogeneity of the disease. Mixed-lineage leukemia-rearrangement (MLL-rearrangement) at 11q23 occurs in at least two-thirds of infants with ALL. The most common MLL rearrangements are t(4;11)(q21;q23)/MLL-AFF1 (AF4) found in approximately 50% of patients.

Methods: Forty children with ALL were enrolled in our study. 11q23 rearrangement and its association with other prognostic factors such as age, sex, initial WBC, organomegaly, immunophenotype, and therapeutic response on the seventh day of induction were studied.

Results: Four patients including three (11.5%) boys and one (7.1%) girl were positive for 11q23 translocation. There was no association between 11q23 rearrangement and sex, age, and initial WBC counts. None of the patients with 11q23 translocation showed blast count less than 5% in the bone marrow on the seventh day of induction (P=0.002).

Conclusion: There was a significant correlation between 11q23 translocation with lack of initial response to chemotherapy.

Keywords: Acute lymphoblastic leukemia, 11q23 translocation, Cytogenetic, Infant acute lymphoblastic leukemia, prognosis, Induction failure

Introduction

Acute lymphoblastic leukemias (ALL) is the most common type of childhood cancer representing 80–85% of all leukemias [1]. ALL in infants often presents with a number of unfavorable clinical features such as hyperleukocytosis, organomegaly, and central nervous system (CNS) involvement [2]. Cytogenetic abnormalities have been described in 80% of childhood ALLs [3,4].

Some chromosomal abnormalities are well known independent prognostic factors in childhood ALL and are used to predict the outcome[5]. Favorable biological characteristics (TEL-AML1 fusion,

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hyperdiploidy) are seldom found in infant ALL whereas myeloid-associated antigen co-expression is a common finding [6,7]. Infantile ALL is commonly associated with MLL gene rearrangements and pro-B (pre-preB/immature/CD10-negative precursor-B) immunophenotype [8].

MLL gene rearrangements arise from fusions of this gene at 11q23 with a large number of partner genes (table 1). In ALL, the most common gene partner is the AF4 gene on chromosome 4q21, resulting in a t(4; 11) (q21; q23) rearrangement[9,10]. It is not clear which of the features associated with infant ALL specifically contribute to the poor therapeutic response [11]. Children with MLL gene abnormalities, and more specifically MLL–AF4 fusion, seem to have a poor prognosis [11,12]. Early in vivo response to treatment (such as prednisolone) was found to be predict the outcome in infant ALL in the German Berlin–Frankfurt–Munster (BFM) studies [13]. However, it is unclear which of the factors (age, MLL rearrangements, or immunophenotype) is most important. The common 11q23 translocation and its partner genes are listed in table 1.

In this study, we aimed to investigate 11q23 rearrangements and their association with other factors such as age, sex, initial WBC, organomegaly, immunophenotype, and therapeutic response. We particularly aimed to assess whether MLL aberrations could be a reliable prognostic factor in childhood ALL.

Patients and Methods

Forty patients with ALL referred to Ahvaz Shafa Hospital during 2012-2013 were enrolled in this study. The study population consisted of a group of children with pre-B ALL that had been diagnosed by morphological and flowcytometric assays and were treated with a similar therapeutic protocol in our institute. In addition, bone marrow samples were obtained on the seventh day of the induction to assess residual blasts. Bone marrow samples were also studied for karyotype and cytogenetic abnormalities.

All procedures involving human participants were in accordance with the ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (REC.1392.209) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Cytogenetic analysis

Preparation of chromosomes was done by bone marrow culture on the slide, i.e. the karyotyping technique. The obtained chromosomes were stained by GIMSA and later denaturalized by trypsin. Then mitosis analysis was done for detecting numerical and structural chromosome aberrations.

Fluorescence in situ hybridization (FISH) analyses

FISH analyses were performed using a locus-specific identifier (LSI) MLL dual-color DNA probe which hybridizes to the MLL gene with a Spectrum Green-labeled probe on the centromeric side (5´) and a spectrum orange-labeled probe to the telomeric side (3´) of the MLL gene breakpoint region. These two signals fuse to one yellow signal in interphase nuclei of normal cells. In cases with MLL rearrangement one yellow signal is present on the normal chromosome 11 and one green and one orange signal are detected on the translocation partner chromosomes.

Descriptive data analysis was conducted using SPSS software. Chi-square test was used to assess the correlation between variables , and $P<0.05$ was considered significant.

Results

Forty infants with ALL were included in this study. All patients immunophenotypically were pre-B ALL. The median age of the patients was 48 months (range: 11-48 months); 26 (65%) of the patients were boys and 14 (35%) were girls. Initial white blood cell (WBC) counts of the patients ranged from 0.1-230×10^9/L (median=23.66×10^9/L). of the 40 studied infants, 12 (30%), two (5%) and four (10%) had splenomegaly, hepatomegaly and hepatosplenomegaly, respectively. FISH analysis showed that 23 (88.5%) boys and 13 (92.9%) girls had no chromosomal abnormalities. Four patients including three (11.5%) boys and one (7.1%) girl were positive for 11q23 translocation. There was no gender difference for 11q23 translocation among these four cases (P=0.6). Likewise, there was no significant difference among patients positive for 11q23 translocation with respect to age (P=0.18).

Considering BFM classification, 23 and 17 patients were diagnosed with L1 and L2 morphology, respectively. Of the four patients who had 11q23

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Table 1: Most frequent translocations of the MLL (11q23) gene in patients with ALL

Translocations	Breakpoint regions	Frequency in ALL patients	MLL fusion partners	Function of partner gene	Outcome	Reference
t(1;11)	(p32;q23) (q21;q23)	Rare	AF-1p AF-1q	Putative signal transduction Growth factor	Poor	(14)
t(4;11)	(q21;q23)	Infant: 50-70% Adult : 3-7%	*A-F4 (AFF1)* FLJ-10849	Transcription activator ?	poor (Age<1: worse outcome)	(4, 5, 15)
t(6;11)	(q21;q23) (q27;q23)	Rare	AF-6q21 AF-6	Transcription factor Signal transduction	Poor	(14)
t(9;11)	(p22;q23) (p34;q23) (p34;q23)	Rare	*MLLT-3*(*AF-9*) AF-9q34 FBP-17	Transcription activator Negative regulator of RAS Telomere maintenance	Poor	(4, 14, 16)
t(10;11)	(p11.2;q23) (p12;q23) (q21;q23)	Rare	ABI-1 AF-10 LCX	Cell growth inhibitor Transcription activator Methyltransferase domain	Poor	(4, 14)
t(11;19)	(q23;p13.1) (q23;p13.3) (q23;p13.3)	13%	ELL EEN ENL	Regulation of cell growth and survival Signal transduction Transcription activator	poor (Age<1: worse outcome Age< 6 months: inferior treatment outcome)	(14, 16)
t(11;17)	(q23;p13) (q23;q21) (q23;q25)	Rare	GAS7 AF17 MSF	Growth-arrest specific protein Transcription factor cycle regulation / Signal transduction	Poor	(14, 16)

MLL: Mixed-lineage leukemia; **AF-1:** Associated factor-1; **FBP-17:** Formin-bindenden Proteins 17; **ABI-1:** Abelson interacting protein 1; **LCX:** Leukemia-associated Protein with a CXXC Domain ; **ELL:** eleven-nineteen lysine-rich leukemia protein ; **EEN:** extra eleven nineteen gene; **ENL:** Eleven Nineteen Leukemia gene; **GAS-7:** growth arrest-specific-7 ; **MSF:** MLL septin-like fusion.

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Table 2: Demographic, clinical and laboratory characteristics of patients with ALL

	Age (month)	Sex	Leukocyte count ($*10^9/L$)	Organomegaly	Morphology	Karyotype	FISH	BMA	CNS
1	51.0	M	27.2	NO	L2	46xy	N	<5%	I
2	48.0	M	39.9	NO	L1	46xy	N	<5%	I
3	36.0	M	49.3	SM	L1	46xy, t(9,11),t(14,22)	N	<5%	I
4	36.0	M	40.7	NO	L1	46xy	N	<5%	I
5	30.0	M	12.7	NO	L1	46xy	P	5-25%	I
6	15.0	F	74.9	NO	L2	46xx, t(4,11)	P	5-25%	I
7	96.0	M	7.4	NO	L1	46xy	N	<5%	I
8	18.0	F	15.4	SM+HM	L1	46xx	N	<5%	II
9	11.0	M	18.3	SM	L1	46xy	N	<5%	I
10	124.0	M	8.7	NO	L2	46xy	N	5-25%	I
11	80.0	F	2.4	NO	L2	46xx	N	5-25%	I
12	73.0	F	3.2	SM	L1	46xx	N	5-25%	I
13	24.0	M	87.5	HM	L2	46xy,del2	N	<5%	I
14	36.0	F	4.8	NO	L1	46xx,t(11;19),del5p	N	<5%	I
15	83.0	M	3.0	NO	L2	46xy,t(1;11)del15	N	<5%	I
16	52.0	F	10.0	NO	L2	46xx	N	<5%	I
17	56.0	M	2.6	SM	L1	46xy,t(11;19),del18	N	<5%	I
18	40.0	M	4.1	NO	L1	46xy,t(4,3)	N	<5%	I
19	124.0	M	1.0	NO	L2	46xy	N	5-25%	I
20	36.0	M	7.7	NO	L2	46xy	N	<5%	I
21	134.0	F	3.2	NO	L1	46xx	N	<5%	I
22	112.0	M	12.2	SM	L2	46xy	P	5-25%	I
23	132.0	F	1.2	NO	L1	46xx	N	<5%	I
24	28.0	F	9.9	SM	L2	46xx	N	5-25%	I
25	12.0	M	122.2	SM+HM	L1	46xy	N	<5%	I
26	148.0	M	2.6	SM	L1	46xy	N	<5%	I
27	57.0	F	11.1	SM	L1	46xx	N	<5%	I
28	60.0	F	11.5	SM	L1	46xx	N	<5%	I
29	52.0	M	23.3	SM+HM	L1	46xy	N	<5%	I
30	12.0	M	4.6	SM		46xy	P	>25%	I
31	26.0	M	1.9	NO	L2	46xy,t(1,14)(p32-34)	N	<5%	I
32	22.0	F	5.3	SM	L1	46xx,inv16(p13;q22)	N	5-25%	I
33	24.0	M	32.0	SM+HM	L2	46xy	N	<5%	I
34	48.0	M	14.8	SM	L2	46xy,t(1,11)	N	<5%	I
35	148.0	M	4.5	NO	L1	46xy,t(1,11)t(4.11)	N	5-25%	I
36	24.0	F	15.5	HM	L2	46xx,t(2,8),t(4,11)	N	<5%	I
37	40.0	M	0.1	NO	L1	46xy	N	<5%	I
38	36.0	F	4.4	NO	L2	46xx	N	5-25%	I
39	72.0	M	230.0	NO	L1	46xx	N	5-25%	II
40	72.0	M	15.3	NO	L2	46xy	N	<5%	I
					L1				

M: Male; **F:** Female; **NO:** No organomegaly; **SM:** Splenomegaly; **HM:** Hepatomegaly; **BM:** bone marrow; **CNS:** central nervous system

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rearrangements, L1 morphology was seen in one and L2 in three cases.

The mean initial WBC counts in patients without 11q23 translocation and those positive for MLL gene rearrangement was 9.3×10^9/L (range: 0.1-230×10^9/L) and 12.4×10^9/L (range: 4600-74900×10^9/L), respectively. There was no significant relationship between WBC count and 11q23 translocation .

By assessing the initial response to chemotherapy based on bone marrow samples obtained on the seventh day of induction, 27 (67.5%) infants had less than 5% blasts, 12 (30%) 5- 25% blasts and one had more than 25% blasts. However, all four patients with 11q23 translocation had more than 5% blasts. There was a positive association between 11q23 translocation and lack of initial response to chemotherapy (P=0.002).

Discussion

There was a significant correlation between 11q23 translocation and lack of initial response to chemotherapy in our study. However, the associations with other variables such as sex, age, and WBC counts were not meaningful. These insignificant results could have also been due to the small sample size of our study.

11q23 translocation is a well known poor prognostic factor which is observed in 2-4% of childhood ALL but is expressed in 80% of infants with ALL[17]. Most children who harbor 11q23 translocations show (4; 11) (q21; q23) abnormality[18].

In a cytogenetic study of cancer cells in 56 children, 21 children indicated t(4,11). Out of 16 patients with a normal karyotype, two cases showed t(1,19) (q32; p13), one case had more than 50 chromosomes and 9 patients had non-recurring structural abnormalities[18]. In a cytogenetic study on 39 infant ALL, 12 (31%) patients had translocation t(4,11)(q21;q23) and EFS was remarkably reduced in these patients. Furthermore, five cases had chromosomal-breakage in 11q23 that this group had longer survival than the previous group. In total, structural disorders were seen in 27 out of 28 patients with abnormal karyotype[19]. In another study, 30 infants suffering from lymphoblastic leukemia were investigated, of which 14 cases had cytogenetic abnormality in 11q23. The results of this study showed that molecular rearrangement in 11q23 specifically has a relationship with adverse prognostic factors such as age less than six months, hyperleukocytosis, CD10-phenotype, and an initial treatment failure[20].

In a large study on 6238 patients with B-precursor ALL, four risk groups were considered and a five-year survival rate was determined and unfavorable prognostic factors were assessed. 11q23 rearrangement was an adverse prognostic factor that put the patients in the high-risk group and was associated with reduced five-year survival rate[21].

In another study on 37 infants with ALL who were less than 18 months old, the effect of 11q23 on prognosis was studied and similar results with previous studies were observed. A total of 18 patients had ALL. Analysis of the results revealed 67% were girls; 50% of them had hyperleukocytosis and 39% had a rearrangement in 11q23. 5-year survival rate of these patients was 14±12%. Nineteen patients had myeloid leukemia and 53% of the cases had rearrangement in 11q23. This group had a very poor prognosis and five-year survival rate was reported to be 20±9%[22].

Raimondi and colleagues studied 785 cases in whom 17 had structural abnormality in the 11q23; 14 patients were del(11)(q23) and three patients showed inv(11)(p12q23). Unlike previous studies, these patients had a better prognosis and fewer leukocytes. This study showed that deletion or reversal in chromosome 11q23 has a better prognosis than patients with 11q23 translocation[23].

In our study, age of the patients was in a higher range than the previous studies. Also on the seventh day of induction all children with 11q23 abnormality had a blast count higher than 5% that represents a poor prognostic factor. Also, it was observed that among patients with 11q23, t(4,11) was among the most common partners of 11q23.

In summary, MLL rearrangements are associated with poor outcome in pediatric ALL. Here we showed an association between 11q23 rearrangement and lack of initial response to chemotherapy, but no relationship was seen between 11q23 translocation with age and sex. Additional molecular and cytogenetic studies on children with ALL in our country considering the ethnicity of Iranian children are needed to precisely find the frequency of MLL gene rearrangements and their correlation with other prognostic factors.

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Conflict of interest disclosure

The authors declare no competing financial interests.

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