Prevalence and Significance of Cytogenetic Findings of Acute Lymphoblastic Leukemia: Experience at King Hussein Medical Center

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ABSTRACT

Objective: To determine the spectrum of cytogenetic abnormalities of acute lymphoblastic leukemia in children and adults at King Hussein Medical Center.

Methods: A retrospective review of raw bone marrow aspirate cytogenetic analysis reports was conducted at Princess Iman Research and Laboratory Sciences Center at King Hussein Medical Center during the period between Jan 2010 and Apr 2014. A total of 97 patients were studied regarding: age, gender, and cytogenetic analysis. The age was categorized into two groups (≤14 years as children group and >14 years as adult group). Descriptive analysis using frequencies was used to describe the study variables.

Results: Fifty-two (53.6%) cases were males and 45 (46.4%) were females. Their ages ranged between six months and 72 years. A total of 72 (74.2%) patients were children and 25 (25.8%) patients were > 14 years old. Of all pediatric acute lymphoblastic leukemia cases, 52.8% (38 cases) were negative for all the cytogenetic abnormalities, while 47.2% (34 cases) revealed one or more cytogenetic abnormalities. Translocation t(12;21), hyperdiploidy (>50 chromosomes or DNA index >1.16) were the predominant cytogenetic abnormalities in children with lymphoblastic leukemia. In the adult lymphoblastic leukemia group, 68.0% (17 cases) were negative for all the cytogenetic abnormalities, while 32% (8 cases) had cytogenetic abnormalities. Hyperdiploidy was the most common (20.0%, 5 patients) followed by translocation t (9;22) (8.0%, 2 patients).

Conclusion: Distribution and patterns of chromosomal abnormalities of lymphoblastic leukemia differ between children and adults. Translocation t(12;21), hyperdiploidy and rearrangements / translocations involving the MLL gene at chromosome 11q23 were the most commonly encountered in children. Hyperdiploidy was prevalent in adults, while no adult cases with 11q23 rearrangements or t(12;21) were encountered.

Key words: Acute lymphoblastic leukemia, Bone marrow aspirate, Cytogenetics.

JRMS September 2015; 22(3): 73-76 / DOI: 10.12816/0013179

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant clonal proliferation of lymphoid progenitor cells, most commonly of the B-cell lineage.[1] ALL in adults remains one of the most

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Manuscript received January 13, 2015. Accepted April 23, 2015

challenging hematological malignancies.[2] On the other hand, ALL is considered as a cancer success story in the pediatric setting.[3] Interestingly, even within adult ALL populations, younger adults have had superior outcomes[4,5] and within pediatric ALL populations, older children have had inferior outcomes.[6] These findings reveal differences between pediatric and adult ALL. Of which, the cytogenetic abnormalities observed in acute lymphoblastic leukemia in children and adults have biologic and prognostic significance.[7]

Recurrent and clonal cytogenetic abnormalities in the blast cells of patients with ALL are essential part of the disease and are now routinely applied in the pediatric ALL to help in patient management, especially in terms of diagnosis, disease monitoring, prognosis, and risk stratification,[8] while the clinical impact of chromosomal abnormalities in adult ALL is an emerging topic, and more studies are urgently needed.[9,10] The 2008 World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues included the detailed ALL-specific chromosomal aberrations and their molecular counterparts.[11]

This study was conducted to study and analyze the spectrum of cytogenetic abnormalities of pediatric and adult acute lymphoblastic leukemia at King Hussein Medical Center.

Methods

This retrospective study was approved by the Ethics Committee of Jordanian Royal Medical Services. We conducted analysis of raw bone marrow aspirate cytogenetic reports at Princess Iman Research and Laboratory Sciences Center at King Hussein Medical Center in Amman-Jordan during the period between Jan 2010 and Apr 2014.

All reports were reviewed regarding: age, gender, and cytogenetic abnormality. The age was categorized into two groups (≤14 years as children group and >14 years as adult group). The cytogenetic Diagnosis was established by Fluorescence in situ hybridization (FISH) which was performed using commercially available DNA probes.

The patients were tested for the presence of numerical chromosomal changes and for three abnormalities, TEL/AML1 fusion t(12;21), BCR/ABL fusion t (9;22) and rearrangements /translocations involving the MLL gene (11q23).

Descriptive analysis using frequencies was used to describe the study variables.

Results

We identified 97 patients who presented with ALL to our center. Fifty-two (53.6%) cases were males. Their ages ranged between six months and 72 years. A total of 72 (74.2%) patients were children (≤ 14 years old) and 25 (25.8%) patients were > 14 years old.

Table I shows, the age distribution of ALL cases according to the yield of the cytogenetic abnormality among the study group. It showed that 47.2% (34 cases). Of all pediatric ALL cases were positive for one or more of the cytogenetic abnormalities, while 32% (8 cases) of adult ALL cases had cytogenetic abnormalities.

Distribution of relative frequencies of specific cytogenetic abnormalities according to the age groups showed that translocation t(12; 21), and hyperdiploidy were the predominant cytogenetic abnormalities in children with ALL and the rearrangement involving the MLL gene (11q23) which was prevalent in infants with ALL (infantile leukemia) constituted 9.7%, while hyperdiploidy followed by translocation t(9; 22) were the most common in adult ALL as illustrated in Table II.

Discussion

One of the most useful prognostic indicators in acute lymphoblastic leukemia (ALL) is cytogenetic studies. A number of recurring chromosomal abnormalities are correlated with distinct Immunophenotypic distribution of ALL and characteristic outcomes.[8,12,13] Our study showed that ALL was predominant in the pediatric age group representing 74.2% as shown in Table I.

This result was comparable to an earlier study done in Iraq by Al-Barazanchi *et al* in 2005 who showed that out of sixty-four newly diagnosed ALL cases, 61% were children (age<15 years), while adults were 39%.[14]

Our study revealed that the frequencies of some cytogenetic abnormalities are substantially different between children and adults with ALL. As Table II showed the t(12; 21), was observed in 15.3% of children with ALL,

Table I: Age distribution of ALL cases according to yield of cytogenetic analysis

Age group	No. (%)	Positive cytogenetic No. (%)	Negative cytogenetic No. (%)
≤ 14 years	72 (74.2)	34 (47.2)	38 (52.8)
>14	25 (25.8)	8 (32.0)	17 (68.0)
total	97	42(43.3)	55 (56.7)

Table II: Age distribution of ALL cases according to specific cytogenetic abnormalities.

Age group	No. (%)	t(12;21) n (%)	Hyperdiploidy n (%)	t(9;22) n (%)	11q23 n (%)	Hyperdiploidy + t(9;22) n (%)	Hyperdiploidy + 11q23 n (%)
≤ 14 years	72 (74.2)	11(15.3)	9 (12.5)	4(5.6)	7(9.7)	2(2.8)	1(1.4)
>14	25 (25.8)	0	5(20)	2(8)	0	1(4)	0
Total	97	11(11.3)	14(14.4)	6(6.2)	7(7.2)	3(3.1)	1(1)

and compared with zero percent of adults.

We also found that the t(9; 22) constituted 5.6 percent of children, compared with 8 percent of adults.

In adult acute lymphoblastic leukemia (ALL), Moorman AV *et al* addressed that pretreatment cytogenetics is generally limited to the presence of the Philadelphia (Ph) chromosome t(9;22) because of the low incidence of other recurrent abnormalities. After revising the cytogenetic data from 1522 adult ALL patients, Moorman AV *et al* showed that patients with t(9;22), t(4;11), t(8;14), complex karyotype (5 or more chromosomal abnormalities), or low hypodiploidy/near triploidy all had inferior outcome when compared with other patients. In contrast, patients with a del (9p) or high hyperdiploidy had significantly improved rates of overall and event-free survival.[10] In the present study, as illustrated in Table II, Hyperdiploidy which is associated with a better outcome accounted for 20% of adults with ALL.

Regarding the relative frequencies of the cytogenetic abnormalities in pediatric ALL, Harrison CJ *et al* evaluated the chromosomal abnormalities of a large, consecutive series of children (n = 2367) with acute lymphoblastic leukemia (ALL) in 2005 and found that t(12;21) (TEL/AML fusion) and t(9;22) (BCR/ABL fusion), and rearrangements of the MLL gene occurred at frequencies of 22% (n = 447/2027) (25% in B-lineage ALL), 2% (n = 43/2027) and 2% (n = 47/2016) respectively.[15] There is agreement between Harrison CJ and our study in terms of predominance of t(12;21) in children with ALL as showed in Table II.

In our study, as showed in table 2, hyperdiploidy constituted 12.5% of the cytogenetic abnormalities of children with ALL. Other studies showed that High hyperdiploidy (51–65 chromosomes) is one of the main cytogenetic abnormalities found in children with B-ALL. It accounts for 25-30% of total childhood B-ALL cases.[16,17] Moorman AV *et al* also addressed the prognostic significance of chromosomal abnormalities as a strong independent indicator in childhood B-cell precursor acute lymphoblastic leukemia outcome. They found that two chromosomal abnormalities were associated with a significantly better outcome t(12;21) and high hyperdiploidy).[18] Fortunately, in our study, t(12;21) and hyperdiploidy were the most common chromosomal abnormalities in childhood ALL at frequencies of 15.3% and 12.5% respectively.

Our study has limitations of being retrospective in nature, including a relatively small number of subjects and representing the experience of a single institution.

Further larger multi-institutional prospective clinical studies are recommended to study the immuno-phenotype of ALL cases and its correlation with the cytogenetic analysis and their outcome in term of relapse and survival, and to consider other cytogenetic abnormalities such as translocation t(1,19).[4,11]

Conclusion

A substantial difference between children and adults with ALL is present. Translocation t(12;21), hyperdiploidy and 11q23

rearrangements were the most commonly encountered in children. Hyperdiploidy was prevalent in adults, followed by translocation t(9;22), while no cases with 11q23 rearrangements or translocation t(12;21) were encountered in adult patients.

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