International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 11(A); November 2018; Page No. 16213-16217
DOI: http://dx.doi.org/10.24327/ijcar.2018.16217.2986

Research Article

COMMON CYTOGENETIC ABNORMALITIES IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AT JINNAH POSTGRADUATE MEDICAL CENTER, KARACHI

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A R T I C L E I N F O

Article History:

Received 13th August, 2018
Received in revised form 11th September, 2018
Accepted 8th October, 2018
Published online 28th November, 2018

Key words:

Cytogenetic abnormalities, acute lymphoblastic leukemia, Philadelphia chromosome

A B S T R A C T

Background: Acute Lymphoblastic Leukemia (ALL) is associated with different structural chromosomal abnormalities and altered chromosomal number which represents its genetic heterogeneity. These aberrations could be both structural or numerical as stated above. Structural aberration alters the chromosome structure but do not involve a change in chromosome number. The mechanism involved rearrangement through loss, gain or reallocation of chromosomal segments. Some patients show a loss or a gain of one or few chromosomes, called aneuploidy. The phenomenon arises due to non-disjunction or abnormal distribution of chromosomes during anaphase of meiosis. If the patient has greater than 49 chromosomes, it is regarded as hyperdiploidy. Whereas, if it is between 35-46, it is regarded as hypodiploidy. These chromosomal abnormalities predict patient outcome and prognosis. Therefore, it is essential to evaluate common cytogenetic abnormalities in patients with acute lymphoblastic leukemia for better and more targeted therapeutic regimes.

Objective: To evaluate the frequency of cytogenetic aberrations in adult patients of Acute Lymphoblastic Leukemia at Medical Oncology Department of Jinnah Postgraduate Medical Center, Karachi, Pakistan to have better understanding of the disease and its course in Pakistani population.

Study Design: Cross sectional, observational study.

Place and Duration of Study: This study was conducted at Oncology Department of Jinnah Postgraduate Medical Center, Karachi from April 2016 to September 2017.

Material and Methods: This was a cross-sectional observational study conducted from April 2016 to September 2017 in Oncology ward of Jinnah Postgraduate Medical Center, Karachi after ethical approval. The total of 32 patients with the age range of 14 to 40 years diagnosed with ALL were included in the study by convenient sampling method. Patients who did not give informed consent and those who had started their treatment were excluded from the study. Complete blood picture and cytogenetic analysis was done by using bone marrow sample from Pathology Laboratory of Aga Khan University Hospital, Karachi. The abnormalities found in cytogenetic analysis were classified into numerical and structural abnormalities. The statistical software SPSS version 20.0 was used for data analysis.

Results: In the total of 32 patients included in the study the mean age of the patients was 23.22±8.37 years with male to female ratio of 3:1. The hemoglobin level (Hb) was 8.49±1.82gm%, red blood cell (RBC) count was 2.87±0.77x106 cells/mm3, haematocrit level was 28.29±4.87%, mean corpuscular volume (MCV) was 87.20±13.84cuμ, mean corpuscular hemoglobin concentration (MCHC) was 28.94±3.57%, white blood cells (WBC) count was 54.22±93.56 x103 cells/mm3 and platelet count was 72.96±77.98 x105cells/mm3. The most common cytogenetics observed was diploidy (two sets of chromosomes) in 28(88%). The two numerical abnormalities were hyperdiploidy (47-57chromosomes) in 2(6%) and hypodipolidy (35-45 chromosomes) in 2(6%). The structural abnormalities were present in combination of translocation, deletion and addition. The most common structural abnormality was translocation (t) found in 29(90.5%) patients. Among them the Philadelphia chromosome t(9;22) was the common translocation found in 8(27.5%), followed by t(q34), t(q11.2), t(q23), t(q25) in 7(24%), 5(17.2%), 3(10.3%), and 2(6.8%) patients respectively. All the other translocations were observed in 1(3.4%) cases. The other structural abnormalities were deletion in 5(15.6%) and addition in 5(15.6%) patients.

Conclusion: This study concluded that majority of adult ALL patients in Pakistan had normal chromosome number. Diploidy was found to be most prevalent and among the abnormalities hyperploidy and hypoploidy were noted in. In structural abnormalities, translocation t(9;22) of chromosome was the most frequent aberration.

INTRODUCTION

Acute leukemia is defined as presence of 20% or greater number of blast cells in the bone marrow or peripheral blood film. Acute lymphoblastic leukemia (ALL) is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites.[1]

Up till now, there is no registry of tumors in Pakistan to seek information for prevalence and incidence of different malignancies including hematological malignancies.[2]

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A fifteen years study conducted in Karachi on children cancers concluded 32% prevalence of ALL in Pakistan.[3] In United States, the overall incidence of ALL is 1.7/100,000 individuals.[4] The risk for developing ALL is highest in children younger than 5 years of age, the risk then declines until the mid-20s and again begins to rise after age 50. Overall, about 4 of every 10 cases of ALL are in adults. The estimated worldwide annual incidence of adult ALL is about one in 100,000.[5]

In ALL, cytogenetic analysis plays a pivotal role in risk stratification and determining the prognosis of disease in patients. Cytogenetics is a branch of genetics that deals with chromosomal study and is concerned with numerical and

structural chromosomal abnormalities. Diagnostic approach towards cytogenetic abnormalities include karyotyping, in situ hybridization, spectral karyotyping, analysis of G-banded chromosomes, and other cytogenetic banding techniques. Karyotype is a standard display of stained and photographed chromosomes, arranged in pairs, in order of decreasing length.[1]

In humans, all somatic cells have diploid number of chromosomes, which means two sets of chromosomes are present in each cell. Cytogenetic abnormalities have been well documented in patients with ALL, including hyperdiploidy and hypodiploidy.[2]

According to the guidelines provided by National Comprehensive Cancer Network (NCCN) ALL should meet the following criteria for diagnosis: Greater than 20% bone marrow lymphoblasts, morphological assessment of Wright/Giemsa–stained bone marrow aspirate smears, hematoxylin and eosin (H&E)–stained bone marrow core biopsy and clot sections, and a comprehensive flow cytometric immunophenotyping ALL patients were grouped into three prognostic groups including good risk, intermediate risk, and poor risk group.[4-6]

- The criteria for good risk includes:
- No cytogenetic abnormality
- Age < 30 years
- White blood cell (WBC) count of < 30,000/μL
- Complete remission within 4 weeks

Intermediate risk includes those patients who did neither meet the criteria for good risk nor for poor risk.

- The poor risk criteria of ALL are:
- Cytogenetic abnormality
- Age > 60 years
- Precursor B-cell white blood cells with white blood cell count greater than 100,000/μL
- Failure to achieve complete remission within 4 weeks.[6]

Cytogenetic aberrations in the cases of ALL are stratified into three subgroups according to the prognosis as good and poor as stated above. High level of hyperdiploidy with chromosomes between 51 and 65 and having t(12;21)(p13;q22) is considered as subgroup with good risk and is majorly observed in children. The translocation t(9;22)(q34;q11) is considered a relatively poor prognostic karyotype subgroup which is found primarily in adults. Bone marrow karyotyping in conjunction with cytogenetic techniques has enhanced the sensitivity and precision of identifying the markers for prognosis of ALL in young patients. Still in adults, the role of ALL cytogenetic in prognosis and treatment has been concentrated around the occurrence of Philadelphia (Ph) chromosome that is a product of translocation between chromosome 9 and 22; t(9;22)(q34;q11.2). In adults, overall prevalence of Ph+ ALL is roughly 25%, but it is associated with increasing age and tends to be present in greater than 50% of patients who are 55 years of age and older.

The discovery of tyrosine kinase inhibitors and their role in the Ph+ ALL has changed the outcome of patients with t(9;22). This is determined in UKALLXII/ECOG2993 imatinib study where it was found that inclusion of imatinib in therapeutic regime of Ph+ ALL patients had positive outcome with 3 year survival rate in 50% of the patients.[7]

Although other abnormalities of the chromosomes have been identified in the adult cases of acute lymphoblastic anemia, their occurrence has been minimal with imprecise prognostic significance. In childhood ALL, modern therapeutic regimens produce complete remission in nearly 90% of the patients, with 5 year survival of greater than 80%.[8] On contrary, therapeutic regimens in adult acute lymphoblastic leukemia has proven to show slow remissions. The average survival in patients between 18 and 60 years is 20%-35%.

There is limited data published in Pakistan about the cytogenetics in patients with ALL and more data should be collected and studied to better understand the pattern and demographics of chromosomal abnormalities in ALL in Pakistan.[9] Complex karyotype is adverse prognostic factor in adults with ALL, independent of minimal residual disease status. These findings suggest that pretreatment cytogenetics remain a valuable prognostic tool and thus supports the aim of our study.

MATERIALS AND METHODS

This was a cross sectional observational study conducted at Oncology Department of Jinnah Postgraduate Medical Center (JPMC), Karachi during period of around 21 months i.e; from April 2016 to September 2017. Approval was taken from the Institutional review board of JPMC, Karachi.

A total of 32 patients with the age range of 14 to 40 years with the diagnosis of ALL on bone marrow biopsy were included in the study by convenient sampling method. Due to a small number of patients, sample size could not be calculated. Informed consent was taken from the patients with complete concealment of the data. All subjects who were included in the study had not started the treatment for ALL. The subjects were divided into two age groups. One group contained subjects who were younger than 30 years of age while the other group had subjects older than 30 years. Patients who did not give consent for participation or who had already started the treatment for the disease were excluded from the study. Proformas with incomplete data were also excluded from the analysis. The demographic data including age, gender and ethnicity with the presenting complaint of the patients was documented.

Cytogenetics Analysis

Complete blood picture and cytogenetic analysis was done by using bone marrow trephine biopsy reported by pathology department of Aga Khan University Hospital, Karachi. Analysis was performed on treatment naive bone marrow samples via G-banding techniques. Pretreatment bone marrow samples were cultured using standard culture techniques, after which harvesting was done including incubation, centrifugation and addition of hypotonic solution. After addition of fixative (3:1 methanol to glacial acetic acid) and trypsin treatment, Giemsa staining was performed. Subject slides were examined under microscope and at least 20 mitosis were analyzed where possible. A successful cytogenetic analysis requires the detection of at least 2 or more cells with the same structural change or chromosomal gain, 3 or more cells with the same chromosomal loss in at least 20

metaphases. Cytogenetic analysis was classified on basis of numerical and structural abnormalities. The numerical abnormalities were classified as diploid, hypo-diploid (<46) and hyper-diploid (>47). The structural abnormalities were categorized as translocation, deletion and addition at chromosomes. All the data was recorded via proformas.

SPSS version 20.0 was used for data analysis. Frequencies and percentages were calculated for categorical variables whereas means and standard deviations were calculated for continuous variables. Bar and pie graphs were used to show the frequency of abnormalities.

RESULTS

In the present study, out of 32 patients 24 (75%) were found to be male and 8 (25%) subjects were female. The mean age of subjects was 23.22±8.37 years with male to female ratio of 3:1. 27 (84.4%) of the subjects were younger than 30 years while 5 (15.6%) subjects were older than 30 years. The mean of hemoglobin level (Hb) was 8.49±1.82gm%, red blood cell (RBC) count was 2.87±0.77x10^6, hematocrit level was 28.29±4.87%, mean corpuscular volume (MCV) was 87.20±13.84cuμ, mean corpuscular hemoglobin concentration (MCHC) was 28.94±3.57%, white blood cells (WBC) count was 54.22±93.56 x10^3 and platelet count was 72.96±77.98 x10^5 as summarized in table 1.

Table 1 Demographic variable and complete blood count n=32

Variable	Mean±SD
Age (years)	23.22±8.37
Hemoglobin (gm%)	8.49±1.82
Red Blood cells (x10^6cells/mm^3)	2.87±0.77
Hematocrit (%)	28.29±4.87
Mean Corpuscular Volume (cuμ)	87.20±13.84
Mean Corpuscular hemoglobin concentration (%)	28.94±3.57
White Blood Cells (x10^3cells/ mm^3)	54.22±93.56
Platelets (x10^5cells/ mm^3)	72.96±77.98

The most frequent presenting complaint was fever in 20(62.5%) of the patients including body ache, general weakness, fatigue, bleeding gums and weight loss were found in 13(40.6%), 8(25%), 6(18.7%), 5(15.6%), and 4(12.5%) cases respectively while vertigo was found only in 2(6.3%) patients as presented in figure 1.

The most frequently reported karyotype was diploidy, observed in 28(88%) of the cases, while the two numerical chromosomal abnormalities were hyperdiploidy 2(6%) and hypodiploidy in 2(6%) as shown in figure 2. The structural chromosomal abnormalities were present in combination of translocation, deletion and addition.

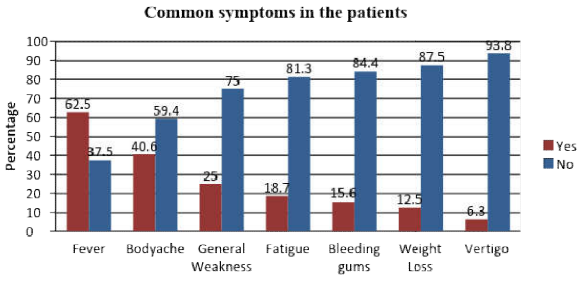

Figure 1

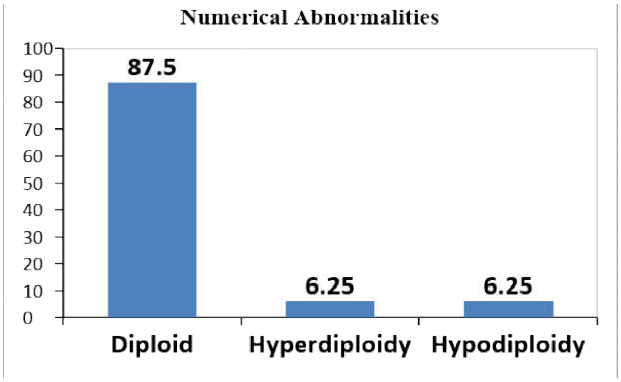

Figure 2

The most common structural abnormality was translocation (t) found in 29(90.5%) patients. Among them the Philadelphia chromosome t(9;22) was the most common translocation found in 8%(27.5%), followed by t(q34), t(q11.2), t(q23) and t(q25) in 7(24%), 5(17.2%), 3(10.3), and 2(6.8%) patients respectively. All the other translocations were observed in 1(3.4%) cases. The additional structural abnormalities were deletion in 5(15.6%) and addition in 5(15.6%) patients. as shown in figure 3.

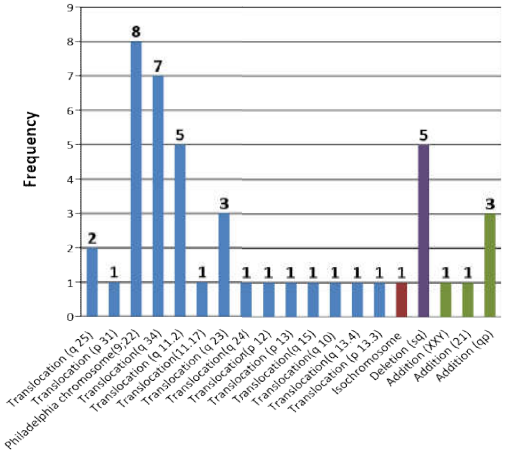

Figure 3 Frequency of different numerical and structural abnormalities

The prognostic groups were made on the basis of age, sex, white blood cell count, cytogenetic abnormality and immunophenotypes. On the basis of these factors the patients were classified as having good or poor prognosis. The female patients who were younger than 30 years, with B-cell type ALL, having a white blood cell count of < 30,000mm3, with a karyotype either hyperdiploid and diploid were classified under good prognosis. Overall only 5 (15.6%) subjects fulfilled the criteria for good prognosis and were categorized as it. On the contrary, the male patients who were older than 30 years in age, suffering from T-cell type ALL, having a white blood cell count of > 30,000mm3, with a hypodiploid karyotype were stratified as poor prognosis. Out of 32, 27 (84.4%) were classified under poor prognostic category. The frequency of patients in category of good prognosis in relation to age, sex, white blood cells count, phenotype and cytogenetic was found to be 27(84.40%), 5 (15.60%), 23 (71.90%), 23 (71.90%), and 18(56.25%) respectively. Similarly it was 5 (15.60%), 27(84.40%), 9 (28.10%), 9 (28.10%) and 14 (43.75%) in the category of poor prognosis as shown in Table 2 and Table 3.

Table 2 Frequency of Patients with Good Prognostic ALL

Good Prognostic Category			
Factors	**Criteria**	**Frequency**	**Percentage**
Age	<30	27	84.40%
Sex	Female	5	15.60%
WBC (mm3)	<30,000	23	71.90%
Phenotype	Non T-cell	23	71.90%
Cytogenetics	Normal or Hyperdiploidy	18	56.25%

Table 3 Frequency of Patients with Bad Prognostic ALL

Factors	Criteria	Frequency	Percentage
Age	>30	5	15.60%
Sex	Male	27	84.4%
WBC (mm^3)	>30,000	9	28.10%
Phenotype	T-cell	9	28.10%
Cytogenetics	Translocation or Hypoploidy	14	43.75%

DISCUSSION

Accurate information in relation to prognosis of Acute Lymphoblastic Leukemia is extremely important before treatment regime is decided upon. Apart from clinical and immunophenotypic prognostic markers, cytogenetics provide reliable information about prognosis which help the clinicians to decide the patients who can attain maximum benefits from the treatment. In the present study, numerical and structural chromosomal aberrations were evaluated and presented in form of frequency and percentages which were identified through karyotyping techniques. In a study, mean age at the time of diagnosis was reported to be 33 years, with a predilection towards the male gender (63%), which is contradictory to our study in which the mean age was 23 years. However, the predominance of male patients in our study is consistent with the above study findings. [10]

In our study, majority of patients with ALL had a presenting complaint of fever 20(62.5%), body pain 13(40.6%) and weakness 8(25%). In a similar study, it was reported that majority of the patients with Acute Lymphoblastic Leukemia presented with fever, generalized weakness, bleeding and weight loss.[2] Another study had similar findings reporting fever to be the chief presenting complaint followed by anemia and bleeding problems.[11] These findings are consistent with our study in which the usual complaint was fever followed by body aches, weakness and fatigue.

In one of the study, adult patients having Acute Lymphoblastic Leukemia with multiple cytogenetic abnormalities were found to have WBC count of $123x10^3$cells/mm^3 (75% lymphoblast) and RBC count of $3.26x10^6$ cells/mm^3 with Hb level of 9.7g/dl and platelet count of $34x10^5$cells/mm^3.[12] In another study, the total WBC count was noted to be 31.1±64. 10^3cells/ mm^3, Hb level 9.0±2.75g/dl and platelet count of $71.7±85.7x10^5$ cells/ mm^3 in adult patients suffering from ALL.[2] In a study on ALL patients, majority of the study population was found to have WBC count above $100x10^3$cells/ mm^3.[13] The finding of this study is in accordance with our results where a decrease in the hemoglobin level, RBC and platelet count of the patients was reported, and an increase in the white blood cell count was also observed.

A study done in Pakistan showed normal karyotype in majority (51%) and abnormal karyotype in less number (49%) of patients.[14] A study conducted at Sindh showed that there were chromosomal abnormalities in 53% of ALL diagnosed patients on cytogenetic testing.[15] An Iranian study documented the frequency of cytogenetic abnormalities for B-ALL and T-ALL patients to be 61.7% and 53.8% respectively, including numerical or structural changes.[16] Whereas in our study chromosomal abnormality was noted in 18(66.25%) of patients while 14(43.75%) of patients had normal karyotype.

In one study, lower incidence of hyperploidy, translocation, deletions were noted.[17] Another study conducted in Pakistan having similar results had hyperploidy occurrence in 6.6% of cases, all being below age 30 years while other cytogenetics with poor prognosis were hypodiploidy and complex karyotype.[14] In another study, diploidy was found in 29%, aneuploidy in 69% of cases and 2% were unknown.[15] In a recent study done in Pakistan, most of the patients showed hyperploidy in 51% followed by hypoploidy in 12% and pseudoploidy in 6% of the cases.[15] According to a study done at Iran, the most common cytogenetic abnormality was hyperploidy in 32%.[16] In our study the hyperploidy and hypoploidy were observed in same frequency of 6% patients.
According to the study in Pakistan the prevalence of Philadelphia chromosome is relatively low in adults having ALL with frequency increasing with advancing age.[14] In another study, chromosomal translocations t(9; 22) (q34; q11) resulting in BCR-ABL fusion was noticed.[15] In one study, the most common structural abnormality in patients was t(9;22) in 11% and the adults showed lower incidence of hyperploidy than of t(9;22). A lower incidence of other translocations 11q23, t(1;19), and t(12;21) and chromosomal structural changes such as deletion 7, deletion 6q, deletion X, duplication 1, and deletion 12p were also found.[16]

A study concluded that survival of adult patients with ALL significantly vary by their age and cytogenetic findings. It has been noted that older age groups and those with t(9;22), t(4;11), low hypoploidy/triploidy or complex karyotype had poor outcomes and were considered as bad prognostic factors.[18] Age was not shown as an important prognostic factor in a study highlighting the finding that variation in karyotyping has major influence on overall survival and relapse free survival in adult ALL patients.[19] However, a contrasting study signified the importance of age as an important prognostic factor. This study stated that patients below 60 years of age have better survival and outcome is same for both genders.[20]
The property of our study is that, we have considered the interpretation of broad variety of chromosomal abnormalities in adult patients suffering from ALL. Conversely, there are selected confounders found in this study such as observer and selection bias. One of the limitations of the study is that a larger sample size could not be accumulated due to time and resource constraints. Considering the observation of our present study, we can establish that there is an association between chromosomal aberrations and ALL, and further research is needed to ascertain this finding.

CONCLUSION

In conclusion, the present study showed that diploidy was the most prevalent karyotype while hyperploidy and hypoploidy were the most prevalent numerical chromosomal aberrations. In 90.5% of the patients, translocation t(9;22)/Philadelphia chromosome was observed in ALL patients. Further research in this field is necessary to culminate any definite disease pattern.

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How to cite this article:

Amna Masood Bhutto *et al* (2018) 'Common Cytogenetic Abnormalities In Patients With Acute Lymphoblastic Leukemia At Jinnah Postgraduate Medical Center, Karachi', *International Journal of Current Advanced Research,* 07(11), pp. 16213-16217. DOI: http://dx.doi.org/10.24327/ijcar.2018.16217.2986

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