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BCR-ABL1 Gene Mutation in Acute Lymphoblastic Leukemia

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Author`s Contribution

[1]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work [2]Final approval of the version to be published [3,4,5]Drafting the work or revising it critically for important intellectual content,[6] Active participation in active methodology

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ABSTRACT

Objective: Determination of frequency of BCR-ABL1 gene mutation in Acute Lymphoblastic Leukemia.

Methodology: This cross sectional study was carried out at the Department of Molecular Haematology, Armed Forces Institute of Pathology between January 2018 to March 2021. All newly diagnosed patients of Acute Lymphoblastic Leukemia were included in the study while patients already on treatment and with secondary leukemia were excluded from the study. Blood counts were done and various parameters such as total leukocyte count, hemoglobin, and platelet count were calculated.

Results: 623 patients were included in the study. BCR-ABL gene was positive in 105 (16.8%) patients. A total of 96 (92%) were positive for BCR ABL p190 rearrangement and 9 (8%) were positive for BCR ABL p210 rearrangement. Mean age of patients was 21 years. The frequency of BCR ABL gene was positive in 72% males and 28% females. BCR-ABL positive ALL was associated with higher TLC count. CNS involvement was more common in Acute Lymphoblastic Leukemia with BCR-ABL. The likelihood of post-induction remission decreased with age.

Conclusion: In our study population, a frequency of 16.8% patients were BCR ABL1 positive in acute lymphoblastic leukemia. BCR- ABL gene mutation in ALL is more prevalent in young adults. The frequency of p190 rearrangement is more common than p210 BCR-ABL rearrangement. BCR-ABL positive ALL is more prevalent in males than in females.

Key words: Acute lymphoblastic leukemia, BCR- ABL gene rearrangement.

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Introduction

Acute lymphoblastic leukemia (ALL) is diagnosed by the presence of over 20% blasts in the bone marrow or the presence of characteristic cytogenetic or molecular abnormality. It is an aggressive disease; if untreated, the clinical course is rapidly downhill. The dominant clinical features are usually related to bone marrow failure caused by accumulation of blast cells. Patient presents with fever, lymphadenopathy, pallor, hepatosplenomegaly and occasionally bleeding tendency.[1]

Increasing research tells us that cytogenetic and molecular abnormalities are present in a large number of patients with ALL. This has resulted in the progress of understanding of genetic characteristics of ALL and many diagnostic centers are now routinely carrying out these tests for the identification of these cytogenetic and molecular abnormalities.[2]

Presently, the WHO criterion for diagnosis and classification of acute lymphoblastic leukemia depends on morphology, immunophenotyping, cytogenetic and molecular analysis. Molecular testing is part of the work up for the classification of acute lymphoblastic leukemia, risk stratification system and the evaluation of prognosis.[3]

The Philadelphia chromosome is a translocation (9; 22), it results in the activation of the BCR/ABL tyrosine

kinase. Among the transcripts of BCR/ABL p190 is the most common in ALL followed by p210. Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is an aggressive disease which responds poorly to conventional chemotherapy. Most of the studies report adverse clinical features and inferior outcomes for patients with BCR-ABL1(+ve) B-ALL, with elevated minimal residual disease levels and poor overall survival as compared with patients with non BCR-ABL+ B-ALL.[4]

With the introduction of tyrosine kinase inhibitors (TKIs), complete hematologic remission has been achieved in vast majority of patients of Ph+ ALL, with improved disease status and overall survival.[4] Many of the patients suffering from ALL who were primarily resistant to induction chemotherapy now screen for BCR ABL1. These patients have shown dramatic responses to ABL-TKIs such as Imatinib and Dasatinib.[5]

Acute lymphoblastic leukemia is associated with several poor prognostic factors which include high TLC, male gender, T-ALL, adult age group, MLL gene rearrangement, CNS disease at presentation and presence of BCR-ABL gene mutation.[6] In this study, we focused on BCR ABL gene mutation frequency in our setup being one of the poor prognostic markers.

In a study conducted at Department of Haematology in Bangabandhu Sheikh Mujib Medical University Dhaka, 38 patients of acute lymphoblastic leukemia were included in which 14 (36.9%) patients were positive for BCR-ABL gene rearrangement.[7] Another study was conducted at Pasteur Institute Iran on 72 patients of ALL in which 9 (12.5%) patient of ALL were positive for BCR-ABL gene rearrangement.[8] These studies being conducted on small sample size showed variation in the results hence we carried out our study in our institute on a large sample size to see the frequency of BCR-ABL gene mutation in diagnosed patients of acute lymphoblastic leukemia.

Our study's rationale is to determine the frequency of BCR-ABL gene mutations in ALL patients in our setup in order to guide clinicians in determining prognosis and tailoring therapeutic regimens accordingly.

Methodology

This cross sectional study was carried out at the department of Molecular Haematology, Armed Forces Institute of Pathology between January 2018 to March 2021. Newly diagnosed patients of Acute Lymphoblastic Leukemia of all ages and both genders were included in the study. All patients who were already receiving treatment for secondary leukaemia were excluded from the study.

Ethical approval was taken from Ethical Committee of Armed Forces Institute of Pathology before the start of research work. 623 patients were included in our study. Informed written consent was taken from all the participants. Demographic data, including age and gender, was recorded. A complete history was taken. The presence or absence of fever, hemorrhage, infections, generalized weakness and anorexia were documented. A physical examination was done, which included lymph nodes examination and presence of hepatosplenomegaly.

Blood counts were done and various parameters such as total leukocyte count, hemoglobin, and platelet count were calculated. Peripheral blood was stained with Leishman stain to check for blast percentage in the peripheral blood. Bone marrow aspiration and trephine biopsy was done for visualizing the blast cells in the bone marrow. CSF R/E was done whenever CNS involvement was suspected. Peripheral blood / bone marrow samples were collected and immunophenotyping by flowcytometry, molecular studies (ALL panel for recurrent genetic mutations) and cytogenetics (karyotyping). Molecular analysis for BCR-ABL gene mutation, RNA was extracted, cDNA prepared and Real time PCR was done for BCR ABL gene mutation using specific primers for each of the fusion transcripts p190 and p210.

Data was analyzed on SPSS version 23. For quantitative variables, the mean and standard deviation was calculated. For qualitative variables frequency and percentage was calculated.

Results

623 newly diagnosed Acute lymphoblastic leukemia patients were recruited in our study. BCR-ABL1 gene mutation was detected in 105 (16.8%) of our study population (Figure 1). Of these BCR-ABL1 positive patients, 97 (92.4%) were positive for the p190 transcript while 8 (7.6%) were positive for p210 transcript (Figure 2). ALL patients harboring the BCR-ABL1 gene mutation were stratified according to age and gender (Figure 3 and Figure 4).

The clinical and haematologic parameters of BCR-ABL1 positive patients at time of diagnosis were compared to

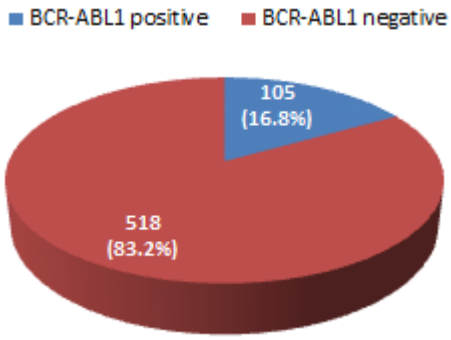

Figure 1. BCR-ABL1 in ALL

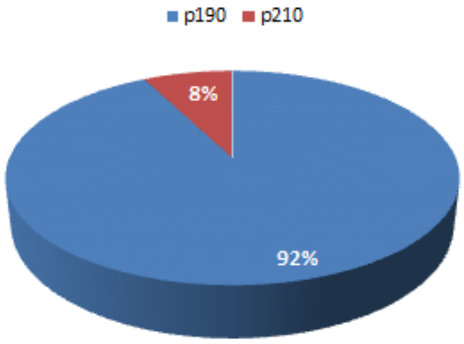

Figure 2. BCR-ABL1 transcripts in ALL. (n=105)

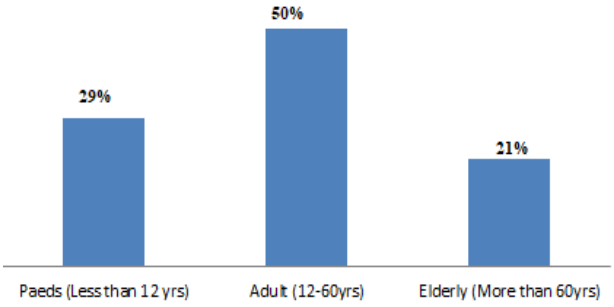

Figure 3. Age Distribution of BCR-ABL1 positive ALL patients

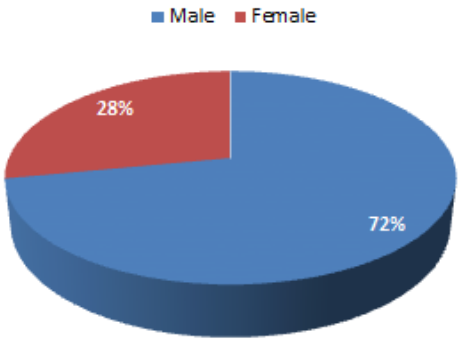

Figure 4. Gender Distribution of BCR-ABL1 positive ALL patients. (n=105)

BCR-ABL1 negative ALL patients (Table I and Table II). CNS involvement was significantly higher in BCR-ABL1 positive ALL patients as compared to BCR-ABL1 negative patients. Significantly high TLC counts correlated with BCR-ABL1 positivity while there was no statistically significant association of Hb levels, platelet count or bone marrow blast percentage with BCR-ABL1 gene mutation.

Table I: Haematologic Parameters of ALL patients.

	BCR ABL (+ve) ALL (n=105)	BCR ABL (+ve) ALL (n=518)
Mean TLC (x 109/L)	79	27
Mean Hemoglobin (g/dl)	6.9	7.1
Mean Platelets (x 109/L)	101	69
Blasts in peripheral blood	40%	70%
Blasts in bone marrow	65%	80%

Table II: Clinical Parameters of ALL patients.

	BCR ABL (+ve) ALL (n=518)	BCR ABL(-ve) ALL (n=518)
Fever	79 (75.2%)	371(71.6%)
Hemorrhage	21(20%)	148(28.6%)
Infections	72(68.6%)	301(58.1%)
Bone pain	44(41.9%)	106(20.5%)
Lymph node	65(61.9%)	207(40%)
Liver/spleen	48(45.7%)	156(30.1%)
CNS involvement	19(18.1%)	21(4.1%)

Discussion

The frequency of BCR ABL gene in acute lymphoblastic leukemia in our study population is comparable to international studies.[8-13] However, it is the largest first-of-its-kind study in Pakistan, conducted in AFIP center.

Year of study	Frequency of BCR ABL gene positivity in Acute lymphblastic leukemia
AFIP (2022)	16.8%
Arana-Trejo (Spain2016)	20%
Azevedo (Brazil 2014)	34%
Foà R (Italy2009)	17%

It is a well known fact that BCR ABL1 positive ALL results in poor prognosis.[14] By documenting the incidence of BCR ABL1 in acute lymphoblastic leukemia patients, oncologists can treat these patients more vigilantly.

In addition to measuring the frequency the following observations were made. BCR- ABL gene mutation in ALL is more prevalent in young adults. Similarly, the frequency of p190 rearrangement is higher than p210 BCR-ABL rearrangement. This observation has also been made in the other studies.[13]

In our study BCR-ABL positive ALL is more prevalent in males than in females. BCR-ABL positive ALL was found to be associated with higher TLC count than BCR ABL negative ALL. CNS involvement was more common in BCR -ABL positive acute lymphoblastic leukemia than BCR- ABL negative acute lymphoblastic leukemia. These findings are also noted in similar studies.[15]

In addition, it was found in our study that the BCR ABL gene mutation tends to be associated mostly with the adult age group, mean age of patients in our study was 21 years. This finding has also been noted in several other studies.[16,17,18] As a result, in young adults, oncologists and haematologists, in particular, must be more vigilant in screening for BCR-ABL gene rearrangement.

Treatment of BCR-ABL positive ALL patients with conventional chemotherapy showed no substantial improvement in long-term outcomes, rather high relapse rates were reported.[19] On the other hand, patients who were treated with tyrosine kinase inhibitors along with chemotherapy showed better results and remission was achieved early with less chances of disease relapse.[20, 21]

Conclusion

In this study population, a frequency of 16.8% patients were BCR ABL1 positive in acute lymphoblastic leukemia. We recommend that all centers involved in diagnosis of acute lymphoblastic leukemia should screen for BCR-ABL1 gene as it is one of the poor prognostic markers. Early documentation will lead to improved treatment outcome and quality of life in these patients.

Disclosure: All the patients were army personnel or dependents of army personnel, who are entitled patients. Facility for these tests is already available at Armed Forces Institute of Pathology for entitled patients.

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