Original Article

ASSOCIATION OF THE PRESENCE OF BCR-ABL1 GENE REARRANGEMENTS AND MYELOID ABERRANT ANTIGENS IN PRECURSOR B-ACUTE LYMPHOBLASTIC LEUKEMIA (PRE-B-ALL) PATIENTS

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ABSTRACT

Objective: To determine the association of the presence of BCR-ABL1 gene rearrangements and myeloid aberrant antigens in precursor B-ALL patients.

Material and Methods: Both males and females, of all age groups, diagnosed with precursor B-ALL on flow cytometry were included in the study. BCR-ABL1 gene rearrangement was identified by performing Fluorescence in situ hybridization (FISH) using Vysis LSI BCR/ABL, Dual color, Dual fusion translocation probe set. The results were noted and compared with the results of flow cytometry.

Results: Male patients were 36 (60%) and female patients were 24 (40%) out of total 60 patients. Median age was 22 years (range 1-73). BCR-ABL1 fusion gene was identified in 47 (78%) patients while 13 (22%) patients were negative for BCR-ABL1. Aberrant myeloid antigens were expressed in 24 (40%) patients and all of these patients were BCR-ABL1 positive. None of BCR-ABL1 negative patients expressed aberrant antigens. There was statistically significant association between BCR-ABL1 positivity and CD117 expression ($P<0.05$).

Conclusion: In developing countries like Pakistan where specialized investigations like cytogenetics are not easily available, the aberrant phenotype can be used as a screening test for predicting the cytogenetics with poor prognosis like BCR-ABL1.

Keywords: BCR-ABL1, Pre-B-ALL, Myeloid aberrant antigens, Flow cytometry, FISH.

This article can be cited as: Younas A, Imtiaz I, Awan MJ, Imran A, Nazir A, Malik NA. Association of the presence of BCR-ABL1 gene rearrangements and myeloid aberrant antigens in precursor B-acute lymphoblastic leukemia (PRE-B-ALL) patients. Pak J Pathol. 2023; 34(4): 118-123.

DOI: 10.55629/pakjpathol.v34i4.786

INTRODUCTION

Acute lymphoblastic leukemia is a clonal hematopoietic disorder that involves the malignant proliferation and accumulation of immature lymphoid cells called lymphoblasts in the peripheral blood, bone marrow and other organs [1]. It is one of the most common childhood malignancies, occurs mainly in children and accounting for more than 20% of childhood leukemias [2]. Though median age at diagnosis is reported to be ≈ 15 years, almost 20% of all leukemia cases in adults are diagnosed as ALL [3].

Based on the origin, ALL is further subdivided into two types. The one that originates from B-cell lineage is B-cell precursor ALL (Pre-B-ALL), accounting for almost 85% of the total diagnosed cases of ALL in pediatric age group and 75% of adult age group [4]. The one that originates from T-cell lineage is T-cell precursor ALL (Pre-T-ALL), that accounts for the remaining 15% of the total cases [5].

The diagnosis of ALL is assessed on the basis of 2016 WHO classification guidelines that combine the cell morphology, immunophenotypes, cytogenetics and molecular characteristics [6]. Flow cytometry is based on the principle that the normal hematopoietic and neoplastic cells express different antigen markers on their surface and cytoplasm [7]. Immunological characteristic of leukemic cells by flow cytometry helps in deciding about the different developmental stages and lineage of malignant cells. Aberrant expression of antigens means abnormal expression of cell specific lineage antigens which is not normally associated with acute leukemia of that specific lineage [8]. Different genetic defects can result in aberrant phenotype expression, that in turn is associated with unfavorable outcome.

A number of genetic alterations and chromosomal abnormalities can occur in Pre-B-ALL, that forms the basis for the updated WHO classification of B-ALL into 2 main classes: B-ALL with recurrent genetic abnormalities and B-ALL not otherwise specified [9]. Among recurrent genetic abnormalities, Philadelphia chromosome t (9;22) with the resultant BCR-ABL1 fusion gene is the most common cytogenetic abnormality associated with Pre-B-ALL [10]. Philadelphia positive pre-B-ALL is an

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*Received:**12 Sep 2023**; Revised: **17 Oct 2023**; Accepted:**14 Dec 2023***

aggressive disease with poor prognosis due to treatment resistance and hence a shorter survival rate. However, the prognosis of Philadelphia positive ALL patients has been significantly improved with the introduction of tyrosine kinase inhibitors (TKIs). There have been studies that showed the possible association between BCR-ABL1 positivity and aberrant myeloid antigen expression in patients of Pre-B-ALL [11,12,13].

In a developing country like Pakistan, little data is available about the incidence of leukemia due to lack of national cancer registry. A collective cancer registry report by Shaukat Khanum memorial cancer hospital and research centre [12] showed that ALL is among the three most common childhood malignancies with 2322 (19.4%) cases of ALL out of total 11943 reported cases from Dec,1994 to Dec, 2022. In a study by Rifat et. Al [14], the results of the Global Cancer Project, conducted in the year 2020 and accessible on https://gco.iarc.fr, showed that leukemia has the highest incidence (4.3 in 1000000) and highest mortality rate (3.4 in 1000000) in Pakistan among South Asian countries.

This high mortality rate may be attributable to the lack of proper diagnostic facilities and timely identification of poor prognostic factors. Though WHO guidelines recommend BCR-ABL1 testing of all the ALL patients for risk stratification, there are only a limited number of tertiary care centers in Pakistan who are following this protocol. This is probably due to high cost and unavailability of cytogenetics at these centers. Our study aims to determine the association of the presence of BCR-ABL1 gene rearrangements and myeloid aberrant antigens in precursor B-ALL patients. Early suspicion about BCR-ABL1 positivity can be made in ALL patients who show aberrant myeloid antigens. This can help in taking decision regarding the addition of TKIs to the routine chemotherapy and in predicting the prognosis of the patients.

MATERIAL AND METHODS

It was a cross sectional analytical study that was conducted at Chughtai institute of Pathology from March 2022 to August 2022. Approval was obtained from the ethical and research committee of the institute. The sample size was calculated by using cochran provided formula that allows us to calculate the ideal minimum sample size from unknown population with a desired confidence level (Z), level of precision (e) and estimated proportion of the disease in the population. In this study, by reviewing the systematic literature [12] and expert opinion, the proportion of ALL in our population is 19% with e=8% and 90% confidence level. By using this value in formula, the minimum sample size of 60 was obtained. Total 60 untreated patients, both males and females, of all age groups, newly diagnosed with precursor B-ALL on fluorescence activated cell sorting (FACS) flow cytometry using BD FACS Lyric analyser, were included in the study. Informed consent was taken from all the patients. Immunophenotypic findings of these patients on flow cytometry were entered in a data sheet. 5ml of peripheral blood sample was taken from each patient in sodium heparin tube following standard procedures. Vysis LSI BCR/ABL, Dual color, Dual fusion translocation probe set was used for the identification of BCR-ABL1 gene rearrangement by FISH. The results were noted and entered in data sheet. Patients with types of leukemia other than ALL, already diagnosed CML patients in blast crisis, patients on chemotherapy and relapsed cases of leukemia were excluded from the study.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-21) for data analysis (SPSS Inc., Chicago, IL, USA). Frequencies and percentages were calculated for categorical variables and mean, median and standard deviation for quantitative variables. Based on the BCR-ABL1 positivity, two groups were created: BCR-ABL1 positive cases and BCR-ABL1 negative cases. Data was checked for normality using Shapiro wilk test. The Fisher's exact tests were used to assess the statistical significance of the different observations between the above-mentioned groups. P value of <0.05 was considered statistically significant.

RESULTS

Out of total 60 patients, 36 (60%) were males and 24 (40%) were females. We included both pediatric and adult patients in our study. Median age was 22 years (range 1-73). BCR-ABL1 fusion gene was identified in 47 (78%) patients while 13 (22%) patients were negative for BCR-ABL1 (Figure-I).

Based on BCR-ABL1 positivity (Figure-III), patients were divided into two groups: BCR-ABL1 positive group and BCR-ABL1 negative group. Immunophenotype results of both groups were noted and compared using Fisher's exact tests. The expression of antigens is measured qualitatively as positive or negative. Comparison of different antigen positivity between BCR-ABL1 positive and BCR-ABL1 negative cases is shown in Table-I.

In the BCR-ABL1 negative group, the most frequently expressed antigens were Tdt, CD79a and CD10 which are present in all the cases (100%), followed by CD19 (92.3%), HLADR and CD34 (both 69.2%) and CD20 (53.8%). None of the cases showed aberrant myeloid antigen expression i.e. CD117, MPO and CD13. In the BCR-ABL1 positive group, again the most frequently expressed antigens were Tdt and CD10 (both 97.8%), followed by CD79a (95.7%), HLADR (91.4%), CD19 (89.3%) and CD34 (80.8%). In contrast to BCR-ABL1 negative group, this group showed significant aberrant myeloid antigen expression (Figure-II) i.e. CD117 positivity in 17 out of 47 cases (36.1%) with a P value of 0.012, and MPO positivity in 5 cases (10.6%) and CD13 positivity in 2 cases only (4.2%) with a P value of 0.575 and 1.000, respectively.

Table-I: Frequency of different markers in BCR-ABL1 positive group and BCR-ABL1 negative group and their comparison with each other. The statistically significant difference of MPO positivity shown in red.

Markers	BCR-ABL1 positive group	BCR-ABL1 negative group	P value
Tdt	46/47 (97.8%)	13/13 (100%)	1.000
CD34	38/47 (80.8%)	9/13 (69.2%)	0.450
CD19	42/47 (89.3%)	12/13 (92.3%)	1.000
CD20	30/47 (63.8%)	7/13 (53.8%)	0.535
CD79a	45/47 (95.7%)	13/13 (100%)	1.000
CD10	46/47 (97.8%)	13/13 (100%)	1.000
CD117	17/47 (36.1%)	0/13 (0%)	**0.012***
MPO	5/47 (10.6%)	0/13 (0%)	0.575
CD13	2/47 (4.2%)	0/13 (0%)	1.000
HLADR	43/47 (91.4%)	9/13 (69.2%)	0.059

Table-II: Comparison of incidence of BCR-ABL1 in ALL patients in Pakistan and other countries.

Authors [Ref.]	Total number of cases	t (9;22) (BCR-ABL1)	Country
Haider *et al*.[17]	**623**	**16.8%**	**Pakistan**
Raza *et al*.[18]	**41**	**85.4%**	**Pakistan**
Iftekhar *et al*.[19]	**150**	**10%**	**Pakistan**
Magatha *et al*.[20]	**84**	**4.8%**	**India**
Velizarova *et al*.[21]	**30**	**17%**	**Turkey**
Carranza *et al*.[22]	**143**	**7%**	**Guatemala**
Azam *et al*.[23]	**38**	**35.7**	**Bangladesh**
Present study	**60**	**78%**	**Pakistan**

Figure-I: Frequency of BCR-ABL1 fusion gene in Pre-B-ALL patients.

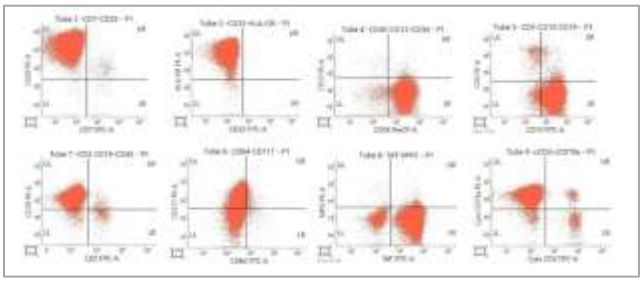

Figure-II: Immunophenotypic results by flow cytometry in a patient with Pre-B-ALL harboring the BCR-ABL1 fusion gene and expressing aberrant myeloid antigen (CD117).

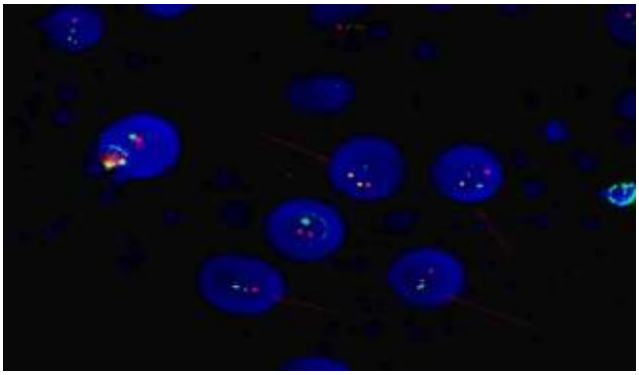

Figure-III: FISH analysis in a Pre-B-ALL patient showing BCR-ABL1 fusion gene. Performed by using Vysis LSI BCR/ABL, Dual Color, Dual fusion translocation probe set: ABL (Red signal), BCR (Green signal), Fusion (Yellow signal) indicated by arrows.

DISCUSSION

In this study, we focused on the evaluation of different cell surface antigens, including aberrant markers, expressed by blast cells in known cases of Pre-B-ALL by flow cytometry and their association with BCR-ABL1 positivity. Many studies have reported the frequency of aberrant myeloid antigens in patients of Pre-B-ALL. In a study by Rezaei *et al*. [1], the most frequently expressed markers were CD19 (100%), HLADR (98.6%), CD79a (96.5%) and Tdt (86.2%). Aberrant myeloid antigens were detected in 7 out of 89 patients of B-ALL (10.1%), out of which CD13 was the most frequently expressed aberrant marker (5.8%), followed by CD33 (2.9%) and CD117 (1.7%). None of the patient expressed MPO. Likewise in our study, the most frequently expressed markers were CD10 (100%) and Tdt (100%), followed by CD79a (95.7%), HLADR (91%) and CD19 (89.3%). In contrast, aberrant myeloid antigen positivity in our study was 36.1% with CD117 being the most frequently expressed aberrant marker (36.1%).

Venugopalan *et al*. [16] investigated aberrant immunophenotype expressions in leukemia patients. In their study, 25% (11/44) of B-ALL patients

expressed aberrant immunophenotypes and the most common aberrancy detected was expression of CD33 (13.6%), followed by CD13 and CD14 expression in 9.1% cases. These results are in contrast to our study as the most commonly expressed aberrant myeloid marker was CD117 (36.1%) in our study.

Cytogenetics have got therapeutic as well as prognostic significance while managing acute leukemias. A number of recurrent genetic abnormalities are found to be associated with B-ALL patients, most common being t (9;22) (BCR-ABL1) with a global incidence of 20-30% [12]. We compared the frequency of BCR-ABL1 fusion gene in B-ALL patients as reported by different studies in Pakistan and other countries in Table-II.

We reported a high incidence (78%) of BCR-ABL1 in Pre-B-ALL patients in our study i.e. comparatively more than that reported in literature. Our results were similar to the results of another study by Raza *et al*. [18], in which the reported incidence was 85.4%, while our results were in contrast to few other studies conducted in Bangladesh [23], Pakistan [17,19], Turkey [21], Guatemala [22] and India [20] which reported relatively lower incidence.

There are a number of studies that reported the association between aberrant myeloid antigen expression and the BCR-ABL1 fusion gene in patients of Pre-B-ALL. Gupta *et al*. [11] used Multiplex RT-PCR assays for detection of recurrent genetic abnormalities and found them in 38.36% (178/464) adult and 20.68% (108/522) pediatric BCP ALL cases. They also found that BCR-ABL1 fusion gene was seen in 31.68% (147/464) adult and 7.08% (37/522) pediatric ALL cases, whereas expression of myeloid antigens was common and observed in 29.0% of BCP-ALL patients, which expressed any one of the myeloid antigens as CD13 [Adults: 47/147 (31.97%), Pediatric: 8/37 (21.62%) P<0.0001], CD33 [Adults: 50/147 (34.01%), Pediatric: 7/37 (18.91%) P<0.0001], and CD117 [Adults: 4/147 (2.72%), Pediatric: 2/37 (5.40%) Statistically not significant]. In comparison, in our study sample size was small and we reported statistically significant association between CD117 expression and BCR-ABL1 positivity (P<0.05) while no association between BCR-ABL1 fusion gene and expression of MPO (P=0.575) and CD13 (P=1.000).

In a study by Tong *et al*. [24], it was demonstrated that B-ALL constitute 78.2% of the total 110 adult patients with ALL. The most common cytogenetic abnormality among 73 patients subjected to karyotype was the Philadelphia (Ph) chromosome, which was found in 23.3% (17/73) of the total cases and 28.8% (17/59) of B-ALL patients. This incidence was lower than reported in our study mainly due to the fact that they analyzed the cases only by routine conventional karyotyping while we used FISH for BCR-ABL1 fusion gene analysis. Myeloid antigen expression was found in 47.3% of the 110 adult ALL cases analyzed and CD13 was the most commonly expressed aberrant antigen in ALL patients (32.1 %). But in contrast to our study, there was no-statistically significant difference observed for expression of aberrant myeloid antigens in Philadelphia positive and Philadelphia negative Pre-B-ALL.

There are many studies conducted in Pakistan that assessed the incidence of BCR-ABL1 in ALL patients and many that described aberrant antigens expression in leukemia patients. In a study by Jawad *et al*. [25], aberrant myeloid expression was observed in 13 (17.8%) out of 73 cases of ALL. Among these, CD13 (11%) and CD33 (12.3%) were most frequently expressed. This is in contrast to our study as 17 out of 47 cases (36.1%) in our study expressed CD117 while only 2 cases (4.2%) expressed CD13. Our results were also in contrast to another study by Shahni *et al* [26] which studied aberrant phenotype in ALL patients and observed this only in seven out of 71 ALL patients. Most frequently expressed aberrant marker in ALL was CD13 and CD33. Also, these were expressed only in T-ALL (CD13, CD33 and HLA-DR) while 2% cases of B-ALL showed co-expression markers of T-cell (CD7) and myeloid origin (CD13 and CD33).

Reported incidence of BCR-ABL1 in Pre-B-ALL patients from Pakistan is lower [27,28], 16-16.8% in both studies, as compared to the incidence reported in our study (78%). Raza *et al* [29] reported high incidence (85.4%) of BCR-ABL1 almost similar to our study.

There is very limited data available that could identify the association between aberrant myeloid antigen expression and BCR-ABL1 fusion gene in Pre-B-ALL patients. Our study is the first in Pakistan that assessed the association between these two and found a statistically significant association between expression of CD117 and BCR-ABL1 fusion gene in Pre-B ALL patients.

CONCLUSION

A hematopathologist should be aware of the aberrant antigens expression while reporting a case of Pre-B-ALL by flow cytometry. This aberrant phenotype can be used as a screening test for predicting the cytogenetics with poorer prognosis like BCR-ABL1 in these patients. In a developing country like Pakistan

where specialized investigations like cytogenetics are not available in all the centers, this can help in assessing the prognosis as well as in managing the patients with targeted therapies like TKIs in addition to chemotherapy.

LIMITATIONS OF THE STUDY

The study was done at a single centre and sample size was also small. Sample size was limited due to cost burden. Larger cohorts with large sample size should be conducted at multiple centers.

CONFLICT OF INTEREST

None

AUTHORS CONTRIBUTION

Ayesha Younas: Literature search, data collection, statistical analysis and article writing

Isma Imtiaz: Literature search and data collection

Mohammad Jamil Awan: Sample analysis by FISH.

Ayisha Imran: Drafted the study design and proof reading

Touqeer Nazir: Data collection and sample collection

Noman Aslam Malik: Overall supervision of the study

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