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Original Article

Post-Induction Remission Status in B-Acute Lymphoblastic Leukemia Patients (B-ALL), Experience at Tertiary Care Hospital

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ABSTRACT

Objectives: To determine the frequency of post-induction remission status and its association with cytogenetic and molecular abnormalities in patients with B-ALL.
Study Design: Cross-sectional Analytical study.
Place and Duration of Study: Armed Forces Institute of Pathology, Rawalpindi Pakistan, from May to Oct 2023.
Methodology: A total of 112 patients who fulfilled the selection criteria were enrolled after written informed consent. All patients underwent cytogenetic and molecular assessment. Patients were treated using regimen-A for standard risk patients and Regimen-B for high-risk patients, in accordance with the UKALL 2011 guidelines. On day 29 of induction treatment, bone marrow was taken once more, post-induction remission was evaluated, and the results were statistically analyzed.
Results: The mean age of the patients was 5.72±3.48 years. Post-induction remission achieved in 93(83%) patients and was significantly associated with no cytogenetic abnormality (p=<0.01), hyperdiploidy (p=0.027) and t(9;22) (p=0.003), with no molecular abnormality (p=0.038) and mutation in BCR-ABL1 (p=<0.01).
Conclusion: Post-induction remission rate was 83% in B-ALL patients. There was significant association of hyperdiploidy with post induction remission; whereas majority patients t(9;22) and BCR-ABL1 failed to achieve post-induction remission.

Keywords: Acute Lymphoblastic Leukaemia, Induction, Remission.

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INTRODUCTION

Acute Leukaemia is a malignant proliferation of blasts, or immature cells.[1] Depending on the lineage of the immature cells, acute leukaemia is traditionally divided into acute myeloid leukaemia and acute lymphoblastic leukaemia. The clonal expansion of lymphoid precursor cells in the blood, bone marrow, and extramedullary locations is known as ALL.[2,3] It is characterized by the replacement of normal haematopoietic component in blood and/or bone marrow by 20% or more blasts of lymphoid origin.[4] It is primarily observed in children with a second peak in the older age range.[5,6] While the course of the disease and its clinical manifestations are well understood, the majority of the data comes from the Western population.[7,8] We share data from our Asian-originated ALL patients here because we believe that regional and ethnic disparities may impact the biology of the disease.

Globally, the yearly incidence of ALL is around 4.75 cases per 100,000 individuals.[9] There is a small observed male preponderance. The illness manifests clinically as an abrupt onset.[10]

Resources are few in underdeveloped nations like Pakistan are limited. Clinico-haematologic factors play a crucial role in risk classification in such environments. The purpose of this study was to obtain insight into the clinical parameters including age and weight, CBC parameters, cytogenetic analysis and molecular studies of our patients with B-ALL and determining its association with post-induction remission (PIR) status. The results of current study would help in the identification of high-risk characteristics and the prediction of treatment response, which will further aid in the making of management decisions meant to enhance patient outcome in a resource restricted country.

METHODOLOGY

The cross sectional analytical study was carried out at the Armed Force Institute of Pathology, Rawalpindi from May to October 2023, after taking approval from the Ethical Review Committee (ERC number: FC-HEM19-14/RED-IRB/22/880). A sample size of 112 patients was calculated keeping, expected frequency of post-induction remission in B-ALL as 82.8%.[2]

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Inclusion Criteria: A total of 112 patients of age 1 to 18 years, of both genders, with newly diagnosed B-Acute lymphoblastic leukemia were included in the study.

Exclusion Criteria: Patients who had received treatment previously i.e. steroids, chemotherapy and radiotherapy and individuals with other malignant tumors were excluded.

Age, gender, results from CBC, aspirate of bone marrow and trephine biopsy, cytogenetic and molecular analysis, immunophenotyping and findings from CSF were among the patient details and laboratory parameters recorded for the study. The automated haematology analyzer was used to do CBC. Following evaluation under light microscopy, the cytological characteristics of the trephine biopsy and bone marrow aspirate were recorded. Flow cytometry was used to both confirm the diagnosis and identify the disease's immunophenotype (i.e. B-ALL).

Remission was defined as percentage of blast in the bone marrow as <5%, absolute neutrophil count (ANC) of more than 1x109 /L, platelet count of more than 100x109 /L, free from transfusion and absent extramedullary involvement (as being confirmed on imaging) at the time of assessment on day 29 of treatment following induction chemotherapy. (WHO 2022). To evaluate cytogenetic anomalies, traditional karyotyping was performed using an automated chromosomal analyzer from MetaSystems. For identification of molecular abnormalities, real-time PCR was used. The patients' CSF was obtained, and it was analysed and also was subjected to cytological evaluation to look for the presence of blast cells in CSF. Based on NCI criteria, patients were classified into two risk groups: standard risk, which included individuals of age 1 to 10 years and TLC less than 50x109 /L, and high risk, which included individuals above 10 years of age and TLC of more than 50X109 /L. Patients were given the UKALL-2011 chemotherapy regimen after their diagnosis were verified. Regimen A, which involved induction with Vincristine, Asparaginase and Dexamethasone, was for patients with standard risk. Regimen B induction, including of Daunorubicin, Asparaginase, Vincristine and Bexamethasone, was administered to high-risk patients. Remission was defined as per WHO 2022 criteria as described above. All findings were noted down by the researcher herself on a predesigned proforma and were subjected to statistical analysis.

Data was analyzed using Statistical Package for social sciences (SPSS) version 25.0. Quantitative data such as age, WBC, ANC, hemoglobin levels and platelet count will be presented as mean and standard deviation. Qualitative variables such as gender, presenting complaints, PIR, cytogenetic abnormalities, molecular abnormalities and NCI risk criteria were presented as frequency and percentages. Association between post-induction remission status and cytogenetic/molecular abnormalities was assessed by using Chi square test and the *p*-value of $\leq$0.05 was considered as significant.

RESULTS

A total of 112 patients were used. The mean age of the patients was 5.72±3.48 years. The mean weight of the patients was 17.76±9.35 kgs. The mean WBC count was 31.07±49.27 x109/L. The mean absolute neutrophil count was 0.48±0.22 x109/L. The mean Hb levels were 7.49±2.91 g/dl. The mean platelet count was 67.11±22.17 x109/L (Table-I).

Table-I: Descriptive Statistics of Study Variables (n=112)

Variables	Mean±SD
Age (in years)	5.72±3.48
Weight (in Kgs)	17.76±9.35
White Blood Cell Count (x109/L)	31.07±49.27
Absolute Neutrophil Count (x109/L)	0.48±0.22
Hemoglobin Levels (in g/dl)	7.49±2.91
Platelet Count (x109 /L)	67.11±22.17

There were 58(51.8%) males and 54(48.2%) females. A total 100(89.3%) patients presented with fever as shown in Table-II. In terms of cytogenetic abnormalities, 81(72.3%) patients did not have any cytogenetic abnormality, 21(18.8%) patients had hyperdiploidy, 7(6.3%) had t(9;22), 2(1.8%) patients had complex abnormalities and 1(0.9%) patient had hypertetraploidy. In terms of molecular abnormality, 91(81.3%) patients had no molecular abnormality, 13(11.6%) patients had mutations in BCL-ABL1, 4(3.6%) patients had mutations in E2A-PBX1, 3(2.7%) patients had mutation in TEL-AML1 and 1 patient had mutation in MLL-MLLT.[10] Post-induction remission occurred in 93(83%) patients (Table-II).

With respect to cytogenetic abnormality, post-induction remission status was significantly associated with no cytogenetic abnormality, hyperdiploidy and t(9;22) as indicated by a *p*-value of <0.01, 0.027 and 0.003, respectively (Table-III). With respect to molecular abnormality, post-induction remission status was significantly associated with no molecular abnormality (p=0.038) and mutation is BCR-ABL1 (p<0.01) (Table-IV).

Table-II: Frequency Distribution of Patient (n=112)

Variables	n(%)
Age Groups:	
1-5 years	72(64.2%)
6-12 years	35(31.3%)
13-18 years	5(4.5%)
Gender:	
Male	58(51.8%)
Female	54(48.2%)
Presenting Complaint:	
Fever	100(89.3%)
Pallor	92(82.1%)
Bruising	19(17%)
Bleeding	8(7.1%)
Lymphadenopathy	48(42.9%)
Bone pain	46(41.1%)
Cytogenetic Abnormalities:	
No abnormality	81(72.3%)
Hyperdiploidy	21(18.8%)
t(9;22)	7(6.3%)
Complex	2(1.8%)
Hypertetraploidy	1(0.9%)
Molecular Abnormalities:	
No defect	91(81.3%)
Mutation in BCR-ACL1	13(11.6%)
Mutation in E2A-PBX1	4(3.6%)
Mutation in TEL-AML1	3(2.7%)
Mutation in MLL-MLLT10	1(0.9%)
Post-induction Remission:	
Yes	93.0(83%)
No	19.0(17%)

Table-III: Association between Cytogenetic Abnormalities and PIR (n=112)

Cytogenetic Abnormalities	Post-Induction Remission		*p*-value
	Yes	No	
No abnormality:			
Yes	74(66.1%)	7(6.2%)	<0.01
No	10(8.9%)	21(18.8%)	
Hyperdiploidy:			
Yes	14(12.5%)	7(6.3%)	0.027
No	79(70.5%)	12(10.7%)	
t(9;22):			
Yes	3(2.7%)	4(3.6%)	0.003
No	90(80.4%)	15(13.4%)	
Complex:			
Yes	1(0.9%)	1(0.9%)	0.209
No	92(82.1%)	18(16.1%)	
Hyper Tetraploidy:			
Yes	1(0.9%)	0(0%)	0.650
No	92(82.1%)	19(17%)	

DISCUSSION

The current study results revealed that in patients with B-ALL, post-induction remission occurred in 83% patients. Majority of the patients were males (51.8%), of age group 1 to 5 years (64.2%). The main presenting complaint was fever (89.3%), pallor (82.1%), lymphadenopathy (42.9%) and bone pains (41.1%). Majority of the patients had no cytogenetic and molecular abnormalities and post-induction remission status was significantly associated with no cytogenetic abnormality (p=<0.01), hyperdiploidy (p=0.027) and t(9;22) (p=0.003), with no molecular abnormality (p=0.038) and mutation in BCR-ABL1 (p=<0.01).

The three main symptoms—neutropenia, thrombocytopenia and anemia. Bruising, fever, exhaustion, and weakness are typical symptoms. Upon examination, individuals may have lymphadenopathy, hepatomegaly and/or splenomegaly in addition to being pale.[11]

Improved outcome for pediatric ALL requires accurate identification of prognostic factors, the determination of risk group and treatment of appropriate duration and intensity according to identified risk group.[12]

Table-IV: Association between Molecular Abnormalities and Post-Induction Remission (n=112)

Molecular Abnormalities	Post-Induction Remission		*p*-value
	Yes	No	
No abnormality:			
Yes	78(69.6%)	12(10.7%)	0.038
No	15(13.4%)	7(6.3%)	
Mutation in BCR-ABL1:			
Yes	7(6.3%)	7(6.3%)	<0.01
No	86(76.8%)	12(10.7%)	
Mutation in E2A-PBX1:			
Yes	4(3.6%)	0(0%)	0.357
No	89(79.5%)	19(17%)	
Mutation in TEL-AML1:			
Yes	3(2.7%)	0(0%)	0.427
No	90(80.4%)	19(17%)	
Mutation in MLL-MLLT10:			
Yes	1(0.9%)	0(0%)	0.650
No	92(82.1%)	19(17%)	

Evidence based prognostic variables include patient factors such as age, initial white blood cell (WBC) count, the genetic and molecular characteristics of disease and individual response to therapy. Risk stratification was traditionally carried out using the white cell count, gender and age.[13] Genetic abnormalities include aneuploidy, recurrent translocations and deletions which are important factors in the determination of risk group. Predictors of excellent prognosis include ETV6-RUNX1 (t(12;21)(p13;q22)) and high hyperdiploidy. Predictors of poor prognosis include BCR-ABL1 (t(9;22)(q34;q11.2)), MLL (or KMT2A)(11q23), and hypodiploidy.[14]

Initial therapy consists of about 4 weeks of remission induction during which steroid (predni-

solone or dexamethasone), vincristine, asparaginase, and intrathecal chemotherapy are given.[15]

The prognosis of patients with B-ALL has significantly improved thanks to years of clinical experience, greater understanding of the underlying disease biology and breakthroughs in therapies.[16]

Our study results revealed that the rate of remission following induction in B-ALL patients was 83%. Similarly, another study conducted in Rawalpindi revealed it to be 89.4%.[17] However, a study conducted by Niaz *et al.,* revealed a higher the post-induction remission rate of 96.6%.[4] Schrappe *et al.,* revealed the post-induction remission rates to be 75%[18] and Maloney *et al.,* revealed it to be 98%.[19] These findings are consistent with our study findings that the rate of post-induction remission is high in patients with B-ALL. B-ALL with high hyperdiploidy, defined to have 51–65 chromosome, is the most common abnormality in childhood ALL. It comprises about 25% of childhood high-risk B-ALL, about 5% of ALL in AYA, and 2–3% of ALL in adults aged >40 years.[20] Hyperdiploidy is considered to have excellent prognosis in patients with B-ALL.[21,22] In our study, patients with hyperdiploidy was seen in 21 patients out of which 14(70%) have achieved post induction remission. Other cytogenetic abnormalities seen in our population were t(9;22) seen in 7(6.3%) patients. Complex cytogenetics and near tetraploid are among rare cytogenetic abnormalities and were seen in 2 and 1 patients respectively. Literature review has described that among the well-established genetic subtypes of B-ALL, t(9;22)(q34;q11), near-haploidy/low hypodiploidy and complex cytogenetics are the high-risk abnormalities with the most impact on treatment and management.[23,24] Similarly in our study, patients with t(9;22) have failed to achieve post induction remission making it a poor prognostic factor.

Among the molecular abnormalities, BCR-ABL1 mutation was seen in 14 patients E2A-PBX1 was seen in 4 patients, TEL-AML1 in 3 and MLL rearrangements were observed in 1 patient. Patients having BCR-ABL1 mutation, which is poor prognostic factors,[25] rate of post induction remission failure was high, making it statistically significant. These findings are consistent with those of Niaz *et al.*,[4] and Rana *et al.*[17]

LIMITATIONS OF STUDY

The current study had few limitations. Firstly, the study was conducted at a single centred and the sample size was limited. A comparatively limited gene panel and the application of traditional cytogenetic analysis were limitations in the molecular characterization of ALL. Long-term follow-up to examine patients' overall and disease-free survival was not performed making it another drawback.

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CONCLUSION

The current study concluded that the post-induction remission rate was 83% in B-ALL patients. The commonest cytogenetic abnormality was Hyperdiploidy and the commonest molecular abnormality was BCR-ABL1. There was significant association between hyperdiploidy, t(9;22) and BCR-ABL1 with post-induction remission. Future studies must be carried out on a larger sample size for validation of current findings.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SI & HMR: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZH & IA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AW & ZZ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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