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Oncology Section

Expression of Aberrant Markers and its Association with Remission Postinduction Therapy in Acute Lymphoblastic Leukaemia and Acute Myeloid Leukaemia

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ABSTRACT

Introduction: Haematological malignancies contribute to a significant number (8.2%) among cancer patientsin India. Bursa-Acute Lymphoblastic Leukaemia (B-ALL), Thymus-Acute Lymphoblastic Leukaemia (T-ALL) and Acute Myeloid Leukaemia (AML) are the three main types of leukaemias distinguished based on flow cytometry. Expression of Cluster of Differentiation (CD) markers of a lineage distinct to the blast population is termed as aberrant expression (expression of B/T cell markers in AML or myeloid markers in ALL). Role of aberrant marker expression in leukaemias remain an enigma till date. Aberrant expression of antigens may be associated with adverse outcomes.

Aim: To study the expression of aberrant markers and their association with the remission status postinduction therapy in ALL and AML.

Materials and Methods: A retrospective cross-sectional study done accessing the medical records of Acute Leukaemia patients admitted from 1st January 2019 to 31st December 2019 at Kidwai Memorial Institute of Oncology, Bengaluru. A total of 144 cases were included of which 86 cases were of AML and 58 cases were ALL. ALL was further divided into B-ALL and T-ALL with 40 and 18 cases respectively, 18 cases of T-ALL and 86 cases of AML were included. Demographic and clinicohaematological parameters were recorded. All quantitative variables were described as Mean {Standard deviation(SD)} and all qualitative variables were depicted as number (proportion). Statistical significance assessed by Chi-square and Fischer-Exact test using Statistical Package for the Social Sciences (SPSS) version 22.0.

Results: Majority of patients belonged to 16-25 years age group with a male preponderance of 58.3%. Aberrant marker expression was associated with the remission status with a p-value of 0.23 and 0.185 in ALL and AML patients respectively and was statistically not significant. While the Chi-square test when applied to the total cases (both ALL and AML combined) the p-value was 0.03 and statistically significant.

Conclusion: Aberrant marker expression might predict poor response to induction therapy in acute leukaemias. However, larger studies are needed to confirm these results.

Keywords: Antigens cluster of differentiation, Haematologic neoplasms, Remission induction, Treatment failure

INTRODUCTION

Haematological malignancies contribute to a significant number (8.2%) of cancer patients in India [1]. They have been recognised and treated as a distinct entity since the beginning because of their differences in aetiopathogenesis, genetics, clinical features, prognosis and response to treatment [2,3]. The prevalence of clinically meaningful haematological neoplasm subtypes lacks clarity owing to complexity of patterns reporting as compared to other cancers [4]. In spite of the progress achieved in the cancer care treatment in other malignancies, the additions to the treatment armamentarium in haematological malignancies still remain only a handful [5,6].

Leukaemias are due to a defect in the process of differentiation of blood forming elements of lymphoid or myeloid lineage [7]. Different Cluster of Differentiation (CD) markers are expressed at different stages of development on both lymphoid and myeloid lineage cells [8]. The identification and immunophenotyping of these markers by flow cytometry helps in both diagnosis and classification of leukaemias [9]. The EGIL (European Group for Immunological Characterisation of Acute Leukaemias) [10] or World Health Organisation (WHO) criteria is used to characterise blasts on the basis of markers associated with B-cell, T-cell, and myeloid lineages depending on how strongly they are associated with a specific lineage [11].

B-Acute Lymphoblastic Leukaemia (ALL), T-ALL and Acute Myeloid Leukaemia (AML) are the three main types of leukaemias distinguished based on flow cytometry. Mixed Phenotypic Acute Leukaemia (MPAL) is another distinct entity where CD markers of more than one lineage are expressed in a single blast population or two discrete populations [10]. Expression of CD markers of a lineage distinct to the blast population is termed as aberrant expression (expression of B/T cell markers in AML or myeloid markers in ALL). Aberrant marker expression may be due to underlying genetic causes [12].

MPAL has a worse prognosis compared to other leukaemias. This is thought to be due to the presence of two different lineage markers. The treatment aimed at one of the lineages might lead to the evolution of blasts of the other lineage. Poor responders are sometimes switched from AML to ALL directed therapies or vice versa and some patients achieve complete response [10,13,14].

Role of aberrant marker expression in leukaemias remains an enigma till date. Aberrant expression of antigens may be associated with adverse outcomes [12]. The authors aimed to study the expression of aberrant markers and their association with the remission status post induction therapy in ALL and AML. The study may lead to identification of poor prognostic biomarkers that may lay foundation for the development of targeted therapies in the future.

MATERIALS AND METHODS

This was a retrospective cross-sectional study done accessing the medical records of patients admitted from January 1, 2019 to December 31, 2019 in leukaemia wards of Kidwai Memorial Institute of Oncology, Bengaluru, India. The study was approved under Institutional Scientific Review Board and Institutional Ethical Committee. (No: KCI/MEC/010/20.August.2019). Informed written consent was obtained from all participants.

Inclusion criteria: Forty cases of B-ALL, 18 cases of T-ALL and 86 cases of AML were identified and included for the study in accordance with the EGIL criteria [10].

Exclusion criteria: All those cases of acute leukaemias, which were not in accordance with the EGIL, and AML-M3 cases were excluded from the study.

Details of age, performance status, haemogram and biochemical parameters at the time of presentation, cytogenetics, treatment regimen used and status of remission post induction were documented. Flow cytometry details and expression of aberrant markers were noted in each case. Flow cytometry was done using a 10 colour, 3 lasers Navios Ex (Beckman Coulter) instrument by a CD45 gating strategy. Antibodies used were CD34, CD1a, CD2, cCD3, CD4, CD5, CD7, CD8, CD19, CD10, CD20, cCD79a, CD117, MPO, CD13, CD33, HLA-DR, CD64, CD11c, CD14 and CD184.

STATISTICAL ANALYSIS

Descriptive and inferential statistical analysis was carried out. Results on continuous measurements were presented as Mean±SD (minimum-maximum) and results on categorical measurements were presented in Number (%). Significance was assessed at 5% level of significance. Chi-square/Fisher-Exact test was used to find the significance of study parameters on categorical scale between two or more groups, nonparametric setting for qualitative data analysis. Fisher-Exact test/Chi-square test with Yates's correction was used when cell samples were very small. The p-value <0.05 was considered significant. The statistical software namely SPSS version 22.0 and R environment version 3.2.2 were used for the analysis of the data.

RESULTS

Majority of patients of ALL (70% B-ALL and 61% T-ALL) were adolescents and belonged to the age group 16-25 years; whereas majority of patients of AML belonged to 16-25 years (35%) and 36-45 years (23%). There was a male predominance in all the three types (55% in B-ALL, 88.9% in T-ALL and 53.5% in AML). Age and sex wise distribution of patients shown in the [Table/Fig-1,2].

Most of the ALL patients presented with either a pancytopenia or a bicytopenia (anaemia+thrombocytopenia) with normal leukocyte counts while most of the AML patients were with bicytopenia and elevated leukocyte counts at diagnosis. Laboratory parameters are shown in the [Table/Fig-3,4].

Cytogenetic results are detailed in the [Table/Fig-5]. A 66 (76.7%) of AML patients had normal karyotype, three patients had a complex karyotype, three patients had t(8;21) and rest had either failed cytogenetics or translocations of undetermined significance. Breakpoint Cluster Region protein (BCR) ABL genes was not done in all patients of B-ALL. However, two cases showed Philadelphia chromosome positivity on conventional karyotyping were given Tab. Imatinib in addition to chemotherapy during induction phase.

Majority (38) of patients received Berlin-Frankfurt-Munich (BFM) 95 protocol, one patient BFM 90 and one patient GMALL protocol for induction treatment of B-ALL. All patients of T-ALL received BFM 95 protocol. Treatment protocols used for AML patients were 3+7 induction, hypomethylating agents and low dose Cytarabine and shown in [Table/Fig-6].

Age (in years)	B-ALL n (%)	T-ALL n (%)	AML n (%)	Total n (%)
16-25	28 (70)	11 (61.1)	30 (34.9)	69 (47.9)
26-35	7 (17.5)	3 (16.7)	15 (17.4)	25 (17.4)
36-45	3 (7.5)	4 (22.2)	20 (23.3)	27 (18.8)
46-55	2 (5)	0	16 (18.6)	18 (12.5)
56-65	0	0	3 (3.5)	3 (2.1)
66-75	0	0	2 (2.3)	2 (1.3)
Total	40 (100)	18 (100)	86 (100)	144 (100)
Mean±SD	24.25±8.50	24.44±8.66	35.22±14.05	30.83±13.22

[Table/Fig-1]: Age distribution of acute leukaemia patients.
Mean age is expressed in years; B-ALL: B cell acute lymphoblastic leukaemia; T-ALL: T cell acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; SD: Standard deviation; N: Number of patients

Gender	B-ALL n (%)	T-ALL n (%)	AML n (%)	Total n (%)
Female	18 (45)	2 (11.1)	40 (46.5)	60 (41.7)
Male	22 (55)	16 (88.9)	46 (53.5)	84 (58.3)
Total	40 (100)	18 (100)	86 (100)	144 (100)

[Table/Fig-2]: Gender distribution of acute leukaemia patients.
p=0.019, significant, Chi-Square test

Variables	B-ALL n (%)	T-ALL n (%)	AML n (%)	Total n (%)	p-value
Haemoglobin (g/dL)					
<7	13 (32.5)	3 (16.7)	45 (52.3)	61 (42.4)	0.001**
7-10	19 (47.5)	9 (50)	37 (43)	65 (45.1)	
>10	8 (20)	6 (33.3)	4 (4.7)	18 (12.5)	
TLC (cells/cumm)					
<4000	8 (20)	1 (5.6)	15 (17.5)	24 (16.6)	0.005**
4000-11000	18 (45)	0	26 (30.2)	44 (30.6)	
<11000-20000	3 (7.5)	2 (11.1)	10 (11.6)	15 (10.4)	
<20000-50000	3 (7.5)	7 (38.9)	14 (16.3)	24 (16.7)	
<50000-100000	6 (15)	4 (22.2)	10 (11.6)	20 (13.9)	
>100000	2 (5)	4 (22.2)	11 (12.8)	17 (11.8)	
Platelet count (cells/cumm)					
<150000	36 (90)	16 (88.8)	84 (97.7)	136 (94.4)	0.046*
150000-300000	4 (10)	1 (5.6)	2 (2.3)	7 (4.9)	
>300000	0 (0)	1 (5.6)	0 (0)	1 (0.7)	

[Table/Fig-3]: Haemogram values of acute leukaemia patients at presentation.
Chi-square/Fisher-Exact test
*p<0.05-Significant; **p<0.001-Strongly significant

Variables	B-ALL (Mean±SD)	T-ALL (Mean±SD)	AML (Mean±SD)	Total (Mean±SD)	p-value
LDH (IU)	690.55±590.59	1356.12±835.38	653.14±447.23	747.17±587.2	<0.001**
Creatinine (mg/dL)	0.71±0.20	0.88±0.47	0.78±0.27	0.77±0.29	0.086
Albumin (gm/dL)	3.91±0.58	3.82±0.43	3.73±0.67	3.79±0.62	0.299
Uric acid (mg/dL)	5.07±1.88	6.54±3.11	4.75±1.92	5.06±2.16	0.005**
Serum calcium (mg/dL)	8.85±0.93	9.32±1.19	8.75±1.18	8.85±1.13	0.155

[Table/Fig-4]: Biochemical parameters of acute leukaemia patients.
LDH: Lactate dehydrogenase expressed in International units; Creatinine expressed in milligram per decilitre; Albumin expressed in gram per decilitre; Uric acid expressed in milligram per decilitre; Serum Calcium expressed in milligram per decilitre; **Strongly Significant [ANOVA]

CYG	B-ALL N (%)	T-ALL N (%)	AML N (%)	Total N (%)
+8, t(9,22)	0	0	2 (2.3)	2 (1.4)
NK	26 (65)	16 (88.8)	61 (70.9)	103 (71.5)
CK	1 (2.5)	0	3 (3.5)	4 (2.7)
Hyperdiploidy	4 (10)	0	0	4 (2.7)
NK, NPM1	0	0	3 (3.5)	3 (2.1)
PH+	1 (2.5)	0	2 (2.3)	3 (2.1)
t(8,21), -Y	0	0	3 (3.5)	3 (2.1)
t(8,21), FLT3-ITD	0	0	3 (3.5)	3 (2.1)
Bcrabl	2 (5)	0	0	2 (1.4)
Del11	0	0	2 (2.3)	2 (1.4)
Del3	0	0	2 (2.3)	2 (1.4)
NK, CEBPA+	0	0	2 (2.3)	2 (1.4)
47XY	1 (2.5)	0	0	1 (0.7)
BCR-ABL	1 (2.5)	0	0	1 (0.7)
del 6	0	1 (5.6)	0	1 (0.7)
del 7	0	0	1 (1.2)	1 (0.7)
dic(9,12)	1 (2.5)	0	0	1 (0.7)
Dic(9,12)	1 (2.5)	0	0	1 (0.7)
dic(9,12), BCR-ABL	1 (2.5)	0	0	1 (0.7)
NK, BCR-ABL	1 (2.5)	0	0	1 (0.7)
t(11,14)	0	1 (5.6)	0	1 (0.7)
t(8,21)	0	0	1 (1.2)	1 (0.7)
TETRAPLOIDY	0	0	1 (1.2)	1 (0.7)
Total	40 (100)	18 (100)	86 (100)	144 (100)

[Table/Fig-5]: Cytogenetic (CYG) pattern of acute leukaemia patients.
NK: Normal karyotype; CK: Complex karyotype; NPM1: Nucleophosmin 1; PH+: Philadelphia chromosome positive; t: Translocation; del: Deletion; dic: Dicentric chromosome; CEBPA: CCAAT enhancer binding protein alpha

Treatment	Number (%)
Nil	2 (2.3)
2xLDAC	11 (12.8)
3+7	54 (62.8)
4xAZA	16 (18.7)
4xDECI	3 (3.4)
Total	86 (100)

[Table/Fig-6]: Treatment Regimens used in AML patients.
LDAC: Low dose Ara C; 3+7- 3 days Daunorubicin (60 mg/m^2) plus seven days of Cytarabine (100 mg/m^2); AZA: Azacitidine; DECI: Decitabine

Among B-ALL 36 (90%) of patients achieved remission by the end of induction treatment while 2 (5%) patients died and 2 (5%) patients failed to achieve remission. 16 (88.9%) patients of T-ALL achieved remission while 1 (5.6%) patient died and 1 (5.6%) patient failed to achieve remission. While in AML, 49 (57%) patients achieved remission, 6 (7%) died, 12 (14%) defaulted treatment and 19 (22%) patients failed to achieve remission. Among those who achieved remission 35 (71%) patients received 3+7 induction therapy, 14 (28.5%) patients received hypomethylating agents (Four cycles Azacitidine/Decitabine) and none received Low Dose Ara-C (LDAC).

Overall 14 (35%), 6 (33%) and 34 (39.5%) number of patients had aberrant CD markers in B-ALL, T-ALL and AML respectively. Most common aberrant markers expressed in B-ALL were CD33, in T-ALL were CD10 and in AML were CD7 and CD19 as shown in the [Table/Fig-7]. In patients who achieved remission aberrant CD markers were expressed in 12 (85.7%), 4 (66.7%) and 20 (58.8%) patients of B-ALL, T-ALL and AML respectively. In those who failed to achieve remission aberrant markers were expressed in 2 (14.3%), 1 (16.7%) and 10 (29.4%) patients of B-ALL, T-ALL and AML, respectively. Interpreting in another way in patients of B-ALL, T-ALL and AML who expressed aberrant CD markers remission was achieved in 12 (85.7%), 5 (83.3%) and 20 (58.8%) number of patients; and in those who didn't express aberrant markers remission was achieved in 24 (92.3%), 12 (100%) and 29 (55.8%) number of patients as shown in the [Table/Fig-8,9]. Aberrant marker expression was associated to the remission status with a p-value of 0.23 and 0.185 in ALL and AML patients, respectively and was statistically not significant. While the Chi-square test when applied to the total cases (both ALL and AML combined) the p-value was 0.03 and statistically significant.

Aberrant marker	B-ALL N (%)	T-ALL N (%)	AML N (%)	Total N (%)
Nil	26 (65)	12 (66.7)	52 (60.5)	90 (62.5)
CD10	0	6 (33.3)	0	6 (4.2)
CD13	2 (5)	0	0	2 (1.4)
CD19	0	0	15 (17.4)	15 (10.4)
CD33	10 (25)	0	0	10 (6.9)
CD4	2 (5)	0	0	2 (1.4)
CD5	0	0	1 (1.2)	1 (0.7)
CD7	0	0	18 (20.9)	18 (12.5)
Total	40 (100)	18 (100)	86 (100)	144 (100)

[Table/Fig-7]: Aberrant marker expression in acute leukaemia patients.
CD: Cluster of differentiation

Remission	B-ALL n (%)	T-ALL n (%)	AML n (%)	Total n (%)
Aberrant CD markers- No				
• No	0	0	9 (17.3)	9 (10)
• Yes	26 (100)	12 (100)	43 (82.7)	81 (90)
➢ Remission	24 (92.3)	12 (100)	29 (55.8)	65 (72.2)
➢ Death	2 (7.7)	0 (0)	3 (5.8)	5 (5.6)
➢ Default	0	0	11 (21.1)	11 (12.2)
• Total	26 (100)	12 (100)	52 (100)	90 (100)
Aberrant CD markers- Yes				
• No	2 (14.3)	1 (16.7)	10 (29.4)	13 (24.1)
• Yes	12 (85.7)	5 (83.3)	24 (70.6)	41 (75.9)
➢ Remission	12 (85.7)	4 (66.6)	20 (58.9)	36 (66.6)
➢ Death	0	1 (16.7)	3 (8.8)	4 (7.4)
➢ Default	0	0	1 (2.9)	1 (1.9)
• Total	14 (100)	6 (100)	34 (100)	54 (100)
All cases				
• Total	40 (100)	18 (100)	86 (100)	144 (100)
• p-value	0.23		0.185	0.03*

[Table/Fig-8]: Remission status and aberrant marker expression in acute leukaemias.
*Statistically significant, Chi-square/Fisher-Exact Test

Remission	B-ALL (n=40)	T-ALL (n=18)	AML (n=86)	Total (n=144)
No	2 (5)	1 (5.6)	19 (22.1)	22 (15.3)
Yes	38 (95)	17 (94.4)	67 (77.9)	122 (84.7)
➢ Remission	36 (90)	16 (88.8)	49 (56.9)	101 (70.1)
➢ Death	2 (5)	1 (5.6)	6 (7)	9 (6.3)
➢ Default	0 (0)	0 (0)	12 (14)	12 (8.3)

[Table/Fig-9]: Remission status in acute leukaemias.

DISCUSSION

In the present study, out of the total 144 cases, 86 cases were AML and 58 cases were ALL. ALL was further divided into B-ALL and T-ALL with 40 and 18 cases respectively. AML was categorised according to French-American-British (FAB) grouping and majority cases were M2 and M4 (41 and 33, respectively). AML-M3 was excluded from the study. The present case case profile is similar to that reported by Sherrer RT et al., and Salem DA and Abd El-Aziz SM while in contrary to Gujral S et al., and Chaudhary A et al., who reported majority

of cases as ALL [15-18]. Complete blood count and karyotyping results were well in accordance with the usual presentation in acute leukaemias patients as per conventional data [19].

The adherence to treatment was excellent in ALL patients and could be explained by both young age at presentation and a good performance status, while 14% of AML patients defaulted treatment. Authors would infer this as a result of poor performance status at the time of diagnosis. The fact that all the defaulted patients were on LDAC treatment supports authors inference as this treatment is generally reserved for patients with poor performance status.

Remission rates of the present study patients were well within the expected rates [20,21]. Around one-third of patients had one or more aberrant marker expression. Most common aberrant markers expressed were CD33, CD10 and CD7/CD19 in B-ALL, T-ALL and AML, respectively. These results of aberrant marker expression contradict the results of Chaudhary A et al., but agree with that of Momani A et al, [18,22].

Correlation of aberrant marker expression was not statistically significant when assessed independently for each of the three types of acute leukaemia. However, when the statistical test was performed for the total number of patients included in the study irrespective of their leukaemia subtype the p-value was 0.03 and was statistically significant. In spite of the well-known biological and prognostic differences between the different types of leukaemias, authors would like to infer these results as a probable contribution of increased sample size on the prediction of significance. In future, well-structured studies and studies with larger sample sizes can give more reliable answers are hoped.

Limitation(s)

Limitations of the present study include; firstly, it was based on cross-sectional data and authors couldn't account for the missing information. Secondly, Philadelphia positivity was not assessed in all B-ALL patients which might influence the remission results largely. Thirdly, molecular typing was not done in most of the AML patients due to financial constraints and hence patients could not be risk stratified as per standard guidelines. Lastly, the present sample size was limited and might have interfered with the results as authors sometimes encountered a cell sample size <5 during comparison tests.

CONCLUSION(S)

Nearly one-third of patients had one or more aberrant marker expression. Most common aberrant markers expressed were CD33, CD10 and CD7/CD19 in B-ALL, T-ALL and AML, respectively. Aberrant marker expression might predict poor response to induction therapy in acute leukaemias. However, larger studies are needed to confirm these results. Studies looking into aberrant marker expression and early relapse might further help in understanding its impact on prognosis.

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