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Original Article

Oncology Section

Cytogenetics in Acute Lymphoblastic Leukaemia Patients: A Retrospective Study from a Teaching Hospital in Karnataka, India

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ABSTRACT

Introduction: Cytogenetic assessment is an essential test in patients with Acute Lymphoblastic Leukaemia (ALL), as it is required for diagnosis, treatment and to know the prognosis. Although these tests are done as standard of care in most of the institutes, there are limited publications from India describing karyotypic abnormalities in ALL patients.

Aim: To assess the various cytogenetic abnormalities encountered in patients suffering from ALL and to know the pattern of chromosomal abnormalities.

Materials and Methods: This retrospective cross-sectional study was conducted at a tertiary care teaching hospital in Karnataka, India. Patients who were diagnosed with ALL based on flow cytometry between January 2017 to June 2021 were included in the study and total 61 patients were evaluated for the cytogenetic findings. The medical records of these 61 patients were reviewed to collect their details like age, sex, immunophenotype and cytogenetic findings.

Results: During flow cytometry analysis, side scatter vs Cluster of Differentiation 45 (CD45) expression strategy was applied. Events with low side scatter and dim CD45 expression (blast gate) was gated. Leukaemias expressing precursor markers (CD34/HLA-DR) along with cytoplasmic/surface CD3 were diagnosed as T-cell Acute Lymphoblastic Leukaemia (T-ALL). Leukaemias with precursor markers along with any two out of three B-cell markers i.e CD19, CD79a or CD10 were diagnosed as B-cell Acute Lymphoblastic Leukaemia (B-ALL). In this study 13 patients out of 35 had normal karyotype and this was the most common cytogenetic finding. The most common cytogenetic abnormality in B-ALL patients was hypodiploidy, but t(9;22) (q34;q11.2) was the most common cytogenetic abnormality in adult patients with B-ALL. Among the patients with T-ALL, only 2 (15.38%) patients had chromosomal abnormalities.

Conclusion: The present study highlights the role of cytogenetics in patients undergoing treatment for ALL. Chromosomal abnormalities like t(9;12) (q13;p11.2), t(X;1) (q13;p36.1) and t(9;15) (p13;q11.2) are novel chromosomal abnormalities which were found in the present study. Long-term follow-up is necessary to identify prognostic implications of such chromosomal abnormalities.

Keywords: Acute leukaemia, Chromosomal abnormalities, Lymphoid neoplasms, Translocations

INTRODUCTION

Acute Lymphoblastic Leukaemia (ALL) is a haematological malignancy characterised by abnormal clonal proliferation of the lymphoid progenitor cells in the bone marrow, blood and extramedullary sites [1]. ALL accounts for 20% of all leukaemias in adults and is the most common leukaemia in childhood (80%) [2]. ALL is diagnosed by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood.

The presence of chromosomal aberrations is the hallmark of ALL [1]. Detection of cytogenetic abnormalities is required for diagnosis, treatment and to know the prognosis in ALL patients [3]. Some of the chromosomal abnormalities are associated with favourable outcomes, which include high hyperdiploidy (51-65 chromosomes). The presence of Philadelphia chromosome and rearrangements of the MLL gene (chromosome 11q23) are associated with poor prognosis [3].

There is limited data on cytogenetics in ALL patients from India [2]. The present study was carried out to fill this lacuna, where the cytogenetic findings in patients with ALL was analysed. The aim of present study was to know whether the pattern of chromosomal abnormalities is same as that reported in western literature or whether there are any abnormalities specifically seen in Indian subcontinent.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at SDM College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara University, Dharwad, in Karnataka, India. This study included 61 patients who were morphologically and immunophenotypically diagnosed to have ALL. Though, the study was conducted as per the guidelines of the Ethical Committee of the Institute, but due to Coronavirus Disease-2019 (COVID-19) pandemic situation, getting official permission was not possible. Moreover this study involved only analysis of data which was generated during routine care of patients, hence it was proceeded further.

Patients who were diagnosed as ALL between January 2017 to June 2021 were included in the present study. The data was analysed in January 2022, when all the patients had completed their intensive chemotherapy regimen. The medical records of these 61 patients were reviewed to collect their details like age, sex, clinical history, examination findings, peripheral smear, bone marrow aspiration, bone marrow biopsy, immunophenotype (B-ALL or T-ALL) and cytogenetic findings. This data was collected prior to starting the study to exactly know the inclusion and exclusion criteria for each of the patients.

Bone marrow aspirate samples of these patients were studied by flow cytometry using the machine BD-FACSDiva 8.0.2. An acute leukaemia panel was used to know the immunophenotype which is a diagnostic test for ALL. During flow cytometry analysis side scatter vs CD45 expression strategy was applied. Events with low side scatter and dim CD45 expression (blast gate) was gated. Leukaemias expressing precursor markers (CD34/HLA-DR) along with cytoplasmic/surface CD3 were diagnosed as T-ALL. Leukaemias with precursor markers along with any two out of three B-cell markers i.e CD19, CD79a or CD10 were diagnosed as B-ALL.

Inclusion and Exclusion criteria: Patients who were diagnosed as ALL based on flow cytometry were included in the study. Patients whose cytogenetic test was not done were excluded.

Bone marrow aspirate samples were sent for chromosomal analysis in heparin anticoagulant. Cytogenetic analysis was done on 24 hour

unstimulated cultures on Roswell Park Memorial Institute-1640 (RPMI-1640), Hi-Karyol media. Metaphases were captured at banding resolution of 450-550 with "G bands by Trypsin and Giemsa" (GTG) banding technique. Cytogenetic analysis required the recognition of atleast >2 cells with the same structural change or chromosomal gain, >3 cells with the same chromosomal loss, in atleast 20 metaphases [3]. Karyotype was written according to the International System for Human Cytogenomic Nomenclature (ISCN) [4]. Normal karyotype contains 46 chromosomes. Hypodiploidy is less than 46 chromosomes [5], high hyperdiploidy is presence of 51-65 chromosomes [6]. Low hyperdiploidy is presence of 47-50 chromosomes [7]. Pseudodiploid is presence of 46 chromosomes with structural or numerical abnormalities [8] and hypertriploid is presence of more than 69 chromosomes [9].

STATISTICAL ANALYSIS

Descriptive statistics were used and the data was analysed with number and percentages.

RESULTS

Out of the 61 patients with ALL, 25 (40.99%) were children and 36 (59.01%) were adults. Mean age was 25.39 years (range: 2-69 years). Out of the 61 patients, 35 (57.38%) were males and 26 (42.62%) were females. Male:female ratio was 1.34:1. Age and gender distribution have been summarised in [Table/Fig-1,2] respectively. After immunophenotyping of these cases by flow cytometry, there were 48 (78.69%) cases of B-ALL and 13 (21.31%) cases of T-ALL. Cytogenetic findings in patients with ALL are summarised in [Table/Fig-3]. Chromosomal abnormalities were seen in 22 (36.07%) patients. Normal karyotype was seen in 23 (37.7%) patients. There were no analysable metaphases in 16 (26.23%) patients.

Age (years)	Number of patients	Percentage
≤10	11	18
11-20	20	32.7
21-30	12	19.6
31-40	6	9.8
41-50	5	8.2
51-60	4	6.6
61-70	3	4.9

[Table/Fig-1]: Age-wise distribution of study patients.

Sex	Number of patients	Percentage
Male	35	57.38
Female	26	42.62

[Table/Fig-2]: Gender distribution of study patients.

Cytogenetic findings	Number of patients with ALL (%)	Number of patients with B-ALL (%)	Number of patients with T-ALL
Normal karyotype	23 (37.7%)	16 (33.33%)	7 (53.84%)
Numerical/structural chromosomal abnormalities	22 (36.07%)	20 (41.67%)	2 (15.38%)
No analysable metaphases	16 (26.23%)	12 (25%)	4 (30.76%)
Total	61	48	13

[Table/Fig-3]: Cytogenetic findings of 61 patients with ALL.

B-ALL

The mean age in B-ALL patients was 26.85 years ranging from 2-69 years. Out of 48 patients with B-ALL, 26 (54.16%) were adults and 22 (45.83%) were children and 25 (52.08%) patients were males and 23 (47.92%) were females. Cytogenetic findings in patients with B-ALL are summarised in [Table/Fig-4,5]. Out of total 48 patients, 16 (33.33%) had a normal karyotype (diploid). There were no analysable metaphases in 12 (25%) patients. The t(9;22)(q34;q11.2)/Philadelphia chromosome was found in 4 (8.33%) cases and all were adults. One of the cases had low hyperdiploidy with a co-existent marker chromosome of unknown origin. Another patient had hypodiploidy with monosomy 7 and duplication on the segment between bands 1q21 and 1q42. Other two cases had no other co-existent abnormality. Out of total, 4 (8.33%) of the cases had high hyperdiploidy, 3 of the patients with high hyperdiploidy were children and 1 was an adult. There were no associated structural abnormalities in chromosomes.

In addition to the trisomies and tetrasomies that are usually seen in high hyperdiploidy like +X, +4, +6, +10, +14, +18, +21, +21, there were other trisomies like +1, +5, +7, +8, +11, +13, +15, +19, +20 and +22. Out of all cases of B-ALL, 4 (8.33%) of the cases had low hyperdiploidy [10]. One of the patient with low hyperdiploidy was an adult and had ring chromosome 2 [r(2) (p25q37)] with del (11) (q13q21), monosomy 17 and trisomy 6, 18 and 20, two of the patients were children, one had trisomy 8 and the other had Down syndrome with trisomy 21.

Among all, 5 (10.41%) patients had hypodiploidy (<46 chromosomes) and was found in three children and two adults. The abnormality seen in one of the patient was monosomy 21 and del (6) (q13q23) and was a child. Second patient had t(1;19) (q23;p13.1), derivative chromosome 9 which is formed by unbalanced t(9;15) resulted in a loss of chromosome 15 and was an adult. Third patient had derivative chromosome 9 which is formed by added material of unknown origin on the p arm at band 9p13 along with translocation involving the q arm of the other homologue chromosome 9 and p arm of chromosome 12 at bands 9q13 and 12p11.2 and was a child. Fourth patient was also a child and had derivative chromosome 12 formed by unbalanced translocation involving q arm of chromosome 9 and p arm of chromosome 12 at bands 9q13 and 12p11.2 resulting in loss of chromosome 9.

Pseudodiploid karyotype was found in 7 (14.5%) patients, t(1;19) (q23;p13.1) was found in one patient and both were adults. One of the patient had derivative chromosome 7, which was formed by unbalanced t(7;9) resulted in a loss of chromosome 9. There was co-existing del(10) (p11.2), del(14) (q24), add (16) (p13.3) and add (20) (q13.3) and a marker chromosome and was found in a child. Also, inv (9) (p11q13) was found in one patient and was an adult. One of the patient was found to have a highly complex abnormality which could not be identified and was an adult. Another patient had der (7) add (7) (p13), der (9) add (9) (p13), der (19) t(1;19) (q23;p13.3). This patient was also an adult. One child showed two clones. First clone showed t(X;1) (q13;p36.1) and the second clone showed trisomy 8. One of the patient showed a hypertriploid karyotype and was a child. This patient's karyotype was 70-72,XXX,+1,+3,+5,-15,+21.

T-ALL

Mean age was 20 years ranging from 13-30 years. Out of the 13 patients with T-ALL, 10 (76.92%) were males and 3 (23.07%) were females and 3 (23.07%) patients were children and 10 (76.93%) were adults. A 7 (53.84%) cases had normal karyotype,

Cytogenetic abnormalities	Number of patients (%)	Number of males	Number of females	Number of adults >18 years	Number of children <18 years
Pseudodiploid	7 (14.5%)	4	3	2	5
Low hyperdiploid (47-50 chromosomes)	4 (8.33%)	1	3	2	2
High hyperdiploid (51-65 chromosomes)	4 (8.33%)	3	1	1	3
Hypertriploid (>69 chromosomes)	2 (2.08%)	1	1	1	1
Hypodiploid	5 (10.41%)	3	2	2	3
Total	22	12	10	8	14

[Table/Fig-4]: Distribution of 22 ALL patients based on the number of chromosomes.

Cytogenetic findings	Number of patients (%)	Number of males	Number of females	Number of adults >18 years	Number of children <18 years
t(9;22)(q34;q11.2)	4 (8.33%)	4	0	4	0
t(1;19)(q23;p13.1)	1 (2.08%)	0	1	1	0
der(19)t(1;19)(q23;p13.3)	1 (2.08%)	0	1	1	0
del(6)(q13q23)	1 (2.08%)	1	0	0	1
t(9;12)(q13;p11.2)	1 (2.08%)	0	1	0	1
der(12)t(9;12)(q13;p11.2)	1 (2.08%)	1	0	0	1
dup(1)(q21q42)	1 (2.08%)	1	0	1	0
Inv(9)(p11q13)	1 (2.08%)	0	1	0	1
t(X;1)(q13;p36.1)	1 (2.08%)	0	1	0	1
der(9)t(9;15)(p13;q11.2)	1 (2.08%)	0	1	0	1
der(9)add(9)(p13)	2 (4.16%)	0	2	1	1
der(7)add(7)(p13)	1 (2.08%)	0	1	0	1
der(7)t(7;9)(p13;q13)	1 (2.08%)	1	0	0	1
del(10)(p11.2)	1 (2.08%)	1	0	0	1
del(14)(q24)	1 (2.08%)	1	0	0	1
del(11)(q13q21)	1 (2.08%)	1	0	0	1
add(20)(p13.3)	1 (2.08%)	1	0	0	1
add(16)(p13.3)	1 (2.08%)	0	1	0	1
Total	22	12	10	8	14

[Table/Fig-5]: Distribution of 22 ALL patients based on the structural chromosomal abnormalities.

4 (30.76%) had no analysable metaphases, 2 (15.38%) cases had chromosomal abnormalities like monosomy 10, del (11) (q21) and a marker chromosome. This patient was an adult. Other patient had del (6) (q13q23) and was also an adult.

Follow-up of 27 patients with analysable metaphases are summarised in [Table/Fig-6].

	t(9;22)	Hypodiploidy	46,XX, t(X;1)(q13;p36.1) [15]/47, idem,+8[5] (Low hyperdiploidy)	46, XY with highly complex abnormality	Normal karyotype	Total number of patients
Expired	2	0	1	1	1	5
Relapsed	0	1	1	0	1	3

[Table/Fig-6]: Follow-up of 27 patients. Remaining patients are continuing with treatment and most of them are in maintenance phase of chemotherapy.

Out of these 27 patients five patients expired and three patients had relapsed disease. Out of these five patients who did not show good response two patients had normal karyotype.

DISCUSSION

The Acute Lymphoblastic Leukaemia (ALL) is associated with several cytogenetic abnormalities. Although there are several publications from western countries regarding various cytogenetic abnormalities in ALL, this data is limited in Indian patients [2]. Hence this study was done to fill this lacuna. In this study 23 (37.7%) of the ALL cases had normal karyotype and this was the most common cytogenetic finding. The most common cytogenetic abnormality in B-ALL patients was hypodiploidy. t(9;22)(q34;q11.2) was the most common cytogenetic abnormality in adults among B-ALL patients. Pseudodiploidy, followed by high hyperdiploidy and hypodiploidy were the most common and the second most common chromosomal abnormalities in children with B-ALL, respectively. Among the patients with T-ALL, only 2 (15.38%) patients had chromosomal abnormalities.

According to a study by Reddy P et al., the most common cytogenetic abnormality was high hyperdiploidy and was seen in 12.7% of the ALL cases [2]. Also, in a study conducted by Safaei A et al., 24.2% of the patients with B-ALL were found to have hyperdiploidy [3]. This result is comparatively more when compared to the findings of the present study. However, it is known that karyotyping errors can occur when high hyperdiploidy is investigated by standard cytogenetic techniques [11]. Rest of the findings in B-ALL patients by Safaei A et al., and Bhandari P et al., were slightly variable when compared with the findings in the present study [3,12]. This difference is probably because of the high frequency of failure to find any analysable metaphases. It is well-known that cytogeneticists face several challenges especially in acute lymphoblastic leukaemia due to a low mitotic index and poor morphology of chromosomes [13]. None of the patients in the present study was found to have t(12;21) (p13;q22). This translocation is usually detected by molecular techniques like Real-time Polymerase Chain Reaction (RT-PCR) and Fluorescence In-Situ Hybridisation (FISH) [3].

The presence of ring chromosome 2 is extremely rare [14]. It was also detected in a study conducted by Martineau M et al., in B-ALL patients [15]. The chromosomal rearrangement, deletion, polyploidy or monosomy that can occur in ring chromosomes may possibly lead to formation of fusion proteins resulting in leukemogenesis in B-ALL patients. The presence of del 6(q) is commonly found in both B-ALL and T-ALL patients of paediatric age group. The presence of a possible tumour suppressor gene causing leukaemia has still not been identified at 6q locus [16]. In the present study, del (6) (q13q23) was found in one patient (child) with B-ALL and one patient (adult) with T-ALL. In a study conducted by Safaei A et al., only 1 (0.8%) child had this structural abnormality among the children with B-ALL [3]. Inversion of the chromosome 9, inv (9) (p11q13), is considered as a normal variant by many and was found in one patient in the present study.

In a study conducted by Safaei A et al., there were 46.1% of T-ALL cases and 38.3% of cases with B-ALL having a normal karyotype [3]. Normal karyotype was the most common cytogenetic finding observed even in a study conducted by Reddy P et al., and was seen in 39.7% of the cases [2]. Even though most of the cases were having a normal karyotype, there could be submicroscopic alterations that have resulted in leukaemia.

In the present study, the locus 7p13 was involved in two cases of B-ALL. PURB gene is located at the 7p13 locus and was found in myelodysplastic syndrome patients progressing to acute myeloid leukaemia in a study conducted by Lezon-Geyda K et al., [17]

Knoechel B et al., also detected 7p13 deletion in T-ALL patients [18]. This indicates a possible role of this gene in haematopoiesis.

ABI-1 gene is known to be found at the locus 10p11.2 [19]. Xiong X et al., concluded that there is a tumour suppressor function of ABI-1 gene in prostate [20]. The presence of del (10) (p11.2) was found even in the present study and suggests a possible tumour suppressor function of this gene even in haematopoietic cells.

Chromosomal abnormalities like t(9;12) (q13;p11.2), t(X;1) (q13;p36.1) and t(9;15) (p13;q11.2) were not found in literature and are novel chromosomal abnormalities found in our study.

In the present study, out of 13 patients with T-ALL only one of the patient had (11) (q21). This abnormality was seen even in a study conducted by Ben Abdelali R et al., in 2014 and the patient was a 29-year-old male with T-ALL [21]. In a study conducted by Cocce MC et al., 3 out of 160 T-ALL patients had this structural abnormality [22]. In one of the recent publications by Eulàlia G et al., it was found that presence of complex karyotype, i.e., ≥3 cytogenetic alterations indicated poor prognosis in patients with T-ALL. Such abnormality was found in 8.6% (12/139) patients. Patients with such cytogenetic abnormality had significantly poor response to treatment, event free survival and overall survival [23].

Limitation(s)

The present study had low cohort size; hence, one cannot comment upon the incidence of the new karyotype observed. Further collaborative studies are necessary with larger sample size for better understanding of cytogenetics in ALL patients.

CONCLUSION(S)

The present study highlights the role of cytogenetics in patients undergoing treatment for ALL. Better detection of chromosomal abnormalities by cytogenetics can be possible when we are able to overcome high rate of failure to culture analysable metaphases in ALL and also detect cryptic and submicroscopic genetic abnormalities. Chromosomal abnormalities like t(9;12) (q13;p11.2), t(X;1) (q13;p36.1) and t(9;15) (p13;q11.2) are novel chromosomal abnormalities and were found in the present study. Long-term follow-up is necessary to identify prognostic implications of such chromosomal abnormalities.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jun 13, 2022
- Manual Googling: Sep 10, 2022
- iThenticate Software: Sep 12, 2022 (6%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

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- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

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