Leukemia, Lymphoma, Myeloma

Cytogenetics and Molecular Genetics in Pediatric Acute Lymphoblastic Leukemia (ALL) and Its Correlation with Induction Outcomes

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Abstract

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Aims The aim was to study cytogenetics and molecular genetic profile in pediatric B-acute lymphoblastic leukemia (ALL) and correlate it with induction outcomes.

Subjects and Methods A retrospective study of cytogenetics and molecular genetics of 98 children with B-cell ALL from January 2013 to May 2018 was done. Cytogenetics and molecular genetics were done in the bone marrow using multiplex reverse transcription polymerase chain reaction and G-banded karyotyping, respectively. Minimal residual disease (MRD) assessment was done at the end of induction by flowcytometry.

Results Of the 98 children, 83 (84.6%) had evaluable cytogenetics, with 11 (13.25%) being abnormal karyotypes. Of the 11 abnormal karyotypes, seven children (8.4%) had hyperdiploidy, one had hypodiploidy, and three had miscellaneous findings. In molecular genetics, TEL–AML1 (ETV6/RUNX1)[t(12;21)] was the most common fusion gene abnormality (12.2% [12/98]), followed by E2A–PBX1 [t(1;19)] (5%), BCR/ABL1 [t(9;22)] (3%), and MLL–AF4 [t(4;11)] (1%). All the 98 children attained morphologic remission at the end of induction. All children with hyperdiploidy (7/7) attained remission and MRD negativity, but one expired during maintenance chemotherapy of disseminated tuberculosis. The child with hypodiploidy was MRD-positive. Three (25%) children with t (12;21) were MRD-positive. All children with Ph + ALL, t(1:19), and t (4;11) were MRD-negative. Fifty-two children had no detected abnormalities, six of whom had MRD positivity (11.5%).

Conclusion Cytogenetic and molecular genetic subgrouping prognosticates ALL outcomes. Although 25% of TEL–AML + children had MRD positivity, larger studies are required to validate the same. End-of-induction MRD outcomes did not correlate with chromosomal aberrations.

Keywords

- acute lymphoblastic leukemia
- cytogenetics
- induction
- minimal residual disease
- pediatric

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for about one-quarter of all malignancies in children < 15 years.[1] The annual incidence of ALL in children in various countries ranges from 0.9 to 4.7/100,000 children.[2] Treatment outcome for pediatric ALL is the paradigm of modern research-based treatment, with the current 5-year event-free survival (EFS) approaching 90% compared with virtually zero in the 1950s.[3] Conventionally, the risk factors taken into account for treatment included age, total white cell count at presentation, and initial response to therapy. Recent advances in molecular diagnostics lead to the identification of numerous structural and numerical chromosomal abnormalities in the malignant clones of ALL, some of which have prognostic and therapeutic implications.[4]

Childhood ALL is broadly classified as B-ALL and T-ALL, with each having characteristic recurrent genetic abnormalities. The diagnosis of ALL is based on bone marrow (BM) aspiration, consisting of lymphoblasts comprising more than 25% of all nucleated cells. Further confirmation and classification is by immunophenotyping of the lymphoblastic population into B- and T-ALL. The WHO 2008 classification of B-ALL recognizes a separate category with recurrent genetic abnormalities. Seven genetic abnormalities were included in the 2008 WHO classification, with the 2016 revision adding two more (iAMP21 and BCR-ABL1-like ALL).[5] Usually, the diagnosis of ALL is not made if there are fewer than 20% blasts in the BM aspirate. However, a child may be diagnosed with B-ALL if he/she presents with < 20% of lymphoblasts in the BM and no evidence of an extramedullary mass, but demonstrates one of the known recurring cytogenetic abnormalities associated with B-ALL.[6]

The frequency of chromosomal abnormalities varies among populations, probably due to ethnicity and geographic factors. Conventional karyotyping can identify numerical, structural, and many of the molecular aberrations in the chromosome. However, a few of the clinically and prognostically significant translocations, including t (12:21) (p13: Q22)-ETV6-RUNX1 can be identified only by molecular techniques such as polymerase chain reaction (PCR) or fluorescence in situ hybridization. The presence of the major chromosomal translocations, namely, t(12;21), t(1;19), t(9;22), and t(4;11), defining definite subgroups of B-ALL, represent approximately 30% of all cases in Europe/USA.[7] However, there are geographical differences between the Western and Indian data in the incidence of molecular abnormalities.[8]

Our study is aimed at describing the spectrum of various cytogenetic abnormalities among children with ALL at our center, and studying the response to treatment in terms of BM remission and minimal residual disease (MRD) at the end of induction phase of chemotherapy.

Subjects and Methods

A retrospective descriptive study of molecular cytogenetics of 98 children with B-cell diagnosed since January 2013 was done. Ninety-eight children aged 1 to 18 years (63 males and 35 females; M:F = 1:0.55) with newly diagnosed ALL were studied for molecular cytogenetic analysis. Infants with ALL were excluded from the study, as the biology and treatment protocols were different. Written consent was obtained from the parents of the children. Flow cytometry from either peripheral blood or BM aspiration was done for diagnosing ALL. Children lost to follow-up and who failed to give consent were excluded from the survey. Host factors and clinical parameters were obtained. Detailed clinical examination, investigations, aspiration and examination of BM, chemotherapy (according to risk stratification and as per our institution protocol), and monitoring were conducted as per standard protocol and were not altered. BM was done at the end of induction phase of chemotherapy (on recovery of peripheral blood counts) to look for morphological remission, and the samples were sent for MRD assessment by flow cytometry. Morphological remission was defined as the presence of blasts constituting < 5% of all nucleated cells in the BM aspirate. MRD negativity was defined as blast percentage of < 0.01 of all the nucleated cells.

G-banded karyotyping was done in BM samples to look for chromosome number abnormalities (including hyperdiploidy and hypodiploidy) and gross structural abnormalities. Clinical and hematological findings were collected from files.

For karyotyping, the BM cells were cultured without mitogen in culture medium, supplemented with 15% fetal bovine serum at 37 °C. After incubation, the cells were exposed to colcemid (0.10 µg/mL) for 30 minutes, followed by hypotonic treatment (0.075 M KCl) for 20 minutes, fixed with Carnoy's fixative (methanol:glacial acetic acid 3:1), and kept overnight in a refrigerator. The next day, air-dried slides were made. The chromosomes were G-banded with the trypsin digestion method and stained with Giemsa. All the slides were screened, and available metaphases were analyzed visually. Metaphases of good morphology were captured and analyzed using the Applied Spectral Imaging software. The karyotypes were interpreted, according to the International System for Human Cytogenetic Nomenclature. Favorable cytogenetics included t (12:21) and hyperploidy. Unfavorable cytogenetics included t (9:22), t(4:11), and hypoploidy.

Multiplex reverse transcriptase (RT)-PCR assay was done in peripheral blood/BM samples to confirm/reveal recurrent or cryptic chromosomal rearrangements such as BCR/ABL1 [t (9;22)], ETV6/RUNX1 [t(12;21)], E2A/PBX1 [t(1;19)], and MLL/AF4 [t(4;11)] in the leukocytes. A favorable fusion transcript was ETV6/RUNX1. The identification of E2A/PBX1 [t(1;19)] did not have prognostic importance. BCR/ABL1 [t(9;22)] and MLL/AF4 [t(4;11)] were designated as unfavorable translocations.

Statistical Methods

Fisher's exact test using Prism version 7.02, GraphPad software, La Jolla, California, USA, was used to analyze the proportion of mutations, depending on the type of failure. Analysis of MRD outcomes was done based on Chi-square test, with $p < 0.05$ being considered to be significant.

Results

The following host factors and clinical parameters were obtained from the patients.

Age and Sex

The age of patients at the time of diagnosis ranged from 12 months to 16 years, with the mean age of the patients being 4.8 years. The majority of patients were below 10 years of age (93.8%). The majority of patients were male (64.3%), and the male-to-female ratio was 1.8: 1.

Risk Stratification

The majority were classified as standard risk ($n = 52$, 53%); 44 (45%) children were classified as high risk and two children (3%) as intermediate risk.

►Table 1 summarizes molecular and clinical data.

Bone Marrow Cytogenetics

BM sample was sent for culture, followed by karyotyping in 94.8% of the children (93/98). Of the 93 children for whom BM culture was done, metaphase for karyotyping was observed in 83 (84.6%) children. Out of the 83 patients, 11 (13.25%) were found to have abnormal karyotypes, and the rest 72 (86.75%) were normal.

Seven children (7/83, i.e., 8.4% of the children with metaphase karyotyped) had hyperdiploidy. Based on further classification, two children had high hyperdiploidy, one (1/7) had near triploidy, and four (4/7) had hyperdiploidy (►Fig. 1).

Six of the seven children with hyperdiploidy are alive and attained remission at the end of induction. One child had poor initial response to steroids. One female child with hyperdiploidy (57 XXX + 4 + 6 + 8 + 10 + 13 + 14 + 17 + 18 + 21 + 21 in 12 cells and 46 XX in 8 cells) had poor initial response to steroids, attained remission, and was MRD-negative at the end of induction. She expired while on maintenance chemotherapy, due to disseminated tuberculosis within a few days of starting antitubercular therapy.

One male child with hypodiploidy in 8 cells (35–45), hypohaploidy (< 23) in one cell, and normal karyotyping in 7 cells had poor initial response to steroids. He attained remission at the end of induction but was MRD-positive (0.5%). He subsequently completed treatment and is currently in remission at 6-month follow-up.

One child with balanced reciprocal translocation between the short arm of chromosome 15 and short arm of

Table 1 Relative proportions and clinical characteristics of the molecular subgroups of Indian childhood ALL

Parameter	TEL-AML1	BCR-ABL	E2A-PBX1	MLLAF4	Other/none
n (%)	12 (12.24)	3 (3)	5 (5.1)	1 (1)	77 (78.57)
Male/female (*n*)	9 male/3 female	2 male/1 female	2 male/3 female	1 female	52 male/25 female
Male:female ratio	3:1	2:1	0.6:1		2.08
Age range (years)	2–9	2–8.5	2.75–5	2.8	1–16
Age mean (years)	4.7	4.8	3.65	2.8	5
WBC (10^9/l) range	2–140	11.5–420	10.5–79.1	17.04	0.8–190
WBC (10^9/l) mean	24.7	175.8	195.7	17.04	29.36

Abbreviations: ALL, acute lymphoblastic leukemia; WBC, white blood cell.

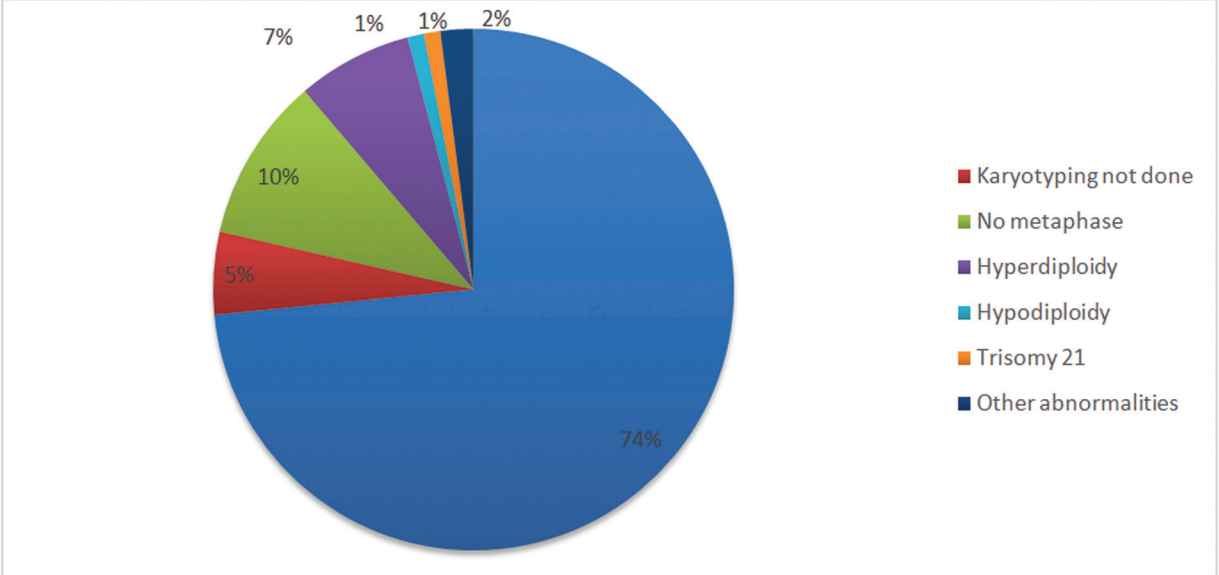

Fig. 1 Frequency of bone marrow (BM) karyotypes.

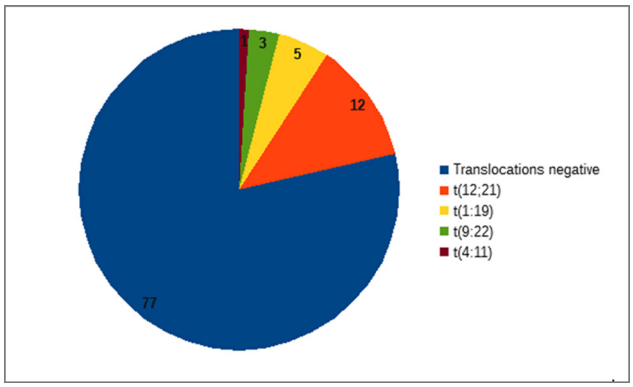

Fig. 2 Relative frequency of abnormal translocations.

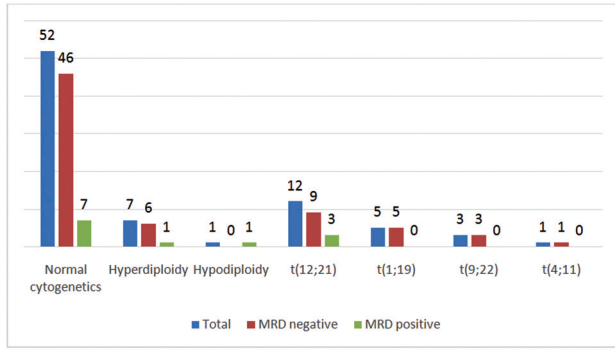

Fig. 3 Minimal residual disease outcomes of children with the various abnormal fusion transcripts and cytogenetics.

chromosome 16 developed isolated central nervous system (CNS) relapse 2 months posttreatment and is currently on salvage chemotherapy.

One child with Down syndrome, who was diagnosed in the newborn period, developed ALL at 11 years of age. He had trisomy 21 in all cells, consistent with his primary diagnosis. He did not have additional chromosomal aberrations.

Molecular Genetics

Molecular analysis was done, and the results were obtained in all the 98 children under study. PCR revealed TEL–AML1, also known as ETV6/RUNX1 [t(12;21)], as the most common fusion gene abnormality, accounting for 12.3% (12/98), followed by E2A–PBX1 [t(1;19)] in 5% (5/98), BCR/ABL1 [t(9;22)] fusion gene in 3% (3/98), and MLL–AF4 [t(4;11)] in 1% (1/98) (►Fig. 2). No abnormal fusion gene was seen in the remaining 77 patients. Notably, all children with TEL–AML1 translocations and one with BCR-ABL fusion transcript had normal BM karyotyping, highlighting the need of combining cytogenetics with molecular genetics for diagnosing cryptic translocations. The characteristics of children based on molecular genetics are summarized in ►Table 1.

Bone Marrow Status and Minimal Residual Disease Outcome at the End of Induction Based on Molecular Genetics

All the 98 children were in complete remission (M1 status of the BM on day 35). Of the children who had normal cytogenetics ($n = 52$), six (11.52%) were MRD-negative at the end of induction. Of the 12 children with ETV6/RUNX1 [t(12;21)], three (25%) were MRD-positive at the end of induction—two had received three drug-based standard risk ALL induction and had to be transferred to high-risk arm in view of MRD positivity. All children with t(1:19) were MRD-negative: four had received standard risk three-drug induction and one had received high-risk induction with four drugs, as the initial response to steroids was poor. The three children with Ph+ ALL received high-risk four drug-based induction along with imatinib and achieved MRD negativity. The child with MLL–AF4 [t(4;11)] received high-risk induction and achieved remission and MRD negativity at the end of induction (►Fig. 3).

There was no statistically significant variation in the end-of-induction MRD outcomes in ALL children with favorable and unfavorable cytogenetics and normal karyotyping/aberrations with nil prognostic importance (►Table 2) (►Fig. 4).

Discussion

Several recurrent chromosomal abnormalities have prognostic significance in precursor B-cell ALL. Some are associated with more favorable outcomes, such as hyperdiploidy and the ETV6–RUNX1 fusion. Others with a poorer prognosis include the Philadelphia chromosome (t(9;22)(q34; q11.2)), rearrangements of the MLL (KMT2A) gene, and hypodiploidy. The genetic aberrations have formed the basis of the recent WHO classification along with the proposed newer molecular abnormalities which are to be incorporated.[5] Our study aimed at studying the relative frequencies of the various chromosomal abnormalities and treatment response at the end-of-induction chemotherapy.

Normal cytogenetics was reported in 72 (86.7%) patients. Hyperdiploidy was the most common numerical chromosomal abnormality (8.4%), which was comparable with studies in India and China.[9–11] However, the incidence of hyperdiploidy in Iran, the US, and Europe is significantly

Table 2 Comparison of minimal residual disease outcomes based on cytogenetics and molecular genetics

Category based on chromosomal aberrations	MRD-positive	MRD-negative	Outcome based on chromosomal aberrations (p)
Favorable ($n = 19$)	4	15	Not significant (0.3065)
Unfavorable ($n = 5$)	1	4	Not significant (0.6105)
None/no prognostic importance ($n = 74$)	7	67	Not significant (0.5639)

Abbreviation: MRD, minimal residual disease.

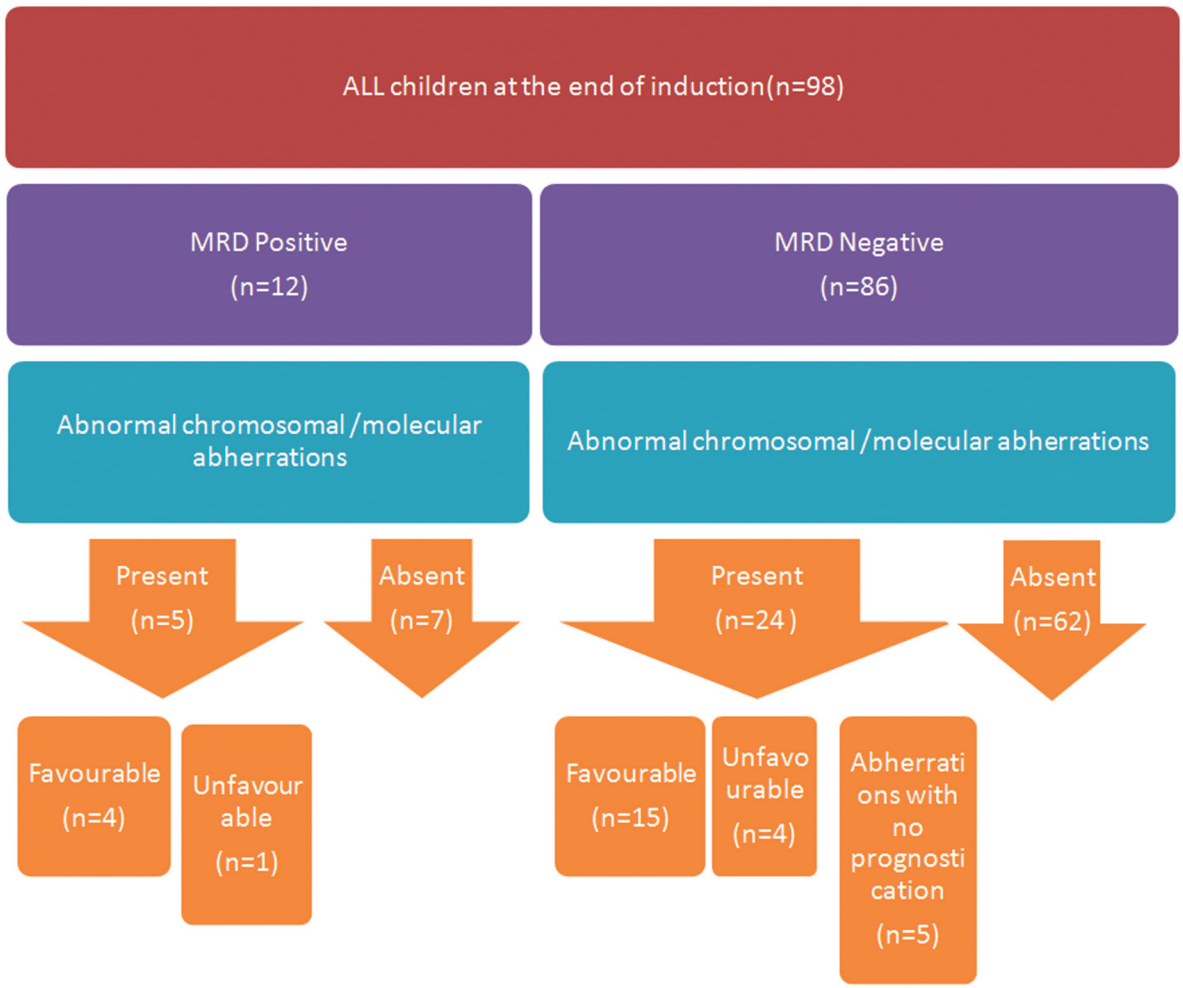

Fig. 4 Distribution of cytogenetic abnormalities among minimal residual disease-positive and -negative children.

higher, ranging from 25.4% in the US to as high as 39% in France.[12–16] The reported incidence of hyperdiploidy in Central and South America is varied (►**Table 3**).[17–20] All the children in the present study had morphological remission at the end of inductions. One child with hyperdiploidy (near triploidy) had MRD positivity at the end of induction and required therapy intensification. Hyperdiploid cases are associated with favorable outcome (5-year EFS > 84%), probably owing to increased accumulation of methotrexate in hyperdiploid blasts.[21] The only child with hypodiploidy had suboptimal response to treatment with poor prednisolone response at day 8 of induction and had MRD positivity at the end of induction. Historical data suggest poor long-term outcomes in children with hypodiploidy.[21] The very low incidence of hypodiploidy in our study is comparable to a report from South India by Mazloumi et al[10] However, the incidence of hypodiploidy from western and northern parts of India is comparatively high.[10,21]

In the present study, the most common chromosomal aberration detected was TEL–AML1 (12.24%), followed by E2A–PBX1 (5%), BCR–ABL (3%), and MLL–AF4. The incidence of t[12;21] in our study is less than the reported incidences in Britain, the US, and Taiwan, but comparable to data from China and France.[12–14,16,18] Although there was a high incidence of MRD positivity in children with TEL–AML1 fusion transcripts, all had morphological remission. Conventionally, children with TEL–AML1 translocation have very good prognosis. However, multivariate analysis of prognostic factors found age and leukocyte count, but not TEL–AML1, to be independent prognostic factors.[22] Long-term follow-up of children with TEL–AML1 confirms the same.[23,24]

The incidence of t(1:19) causing E2A–PBX1 fusion was similar to the reported incidence in several studies from India, approaching approximately 5%.[8,25,26] However, a few Indian studies have reported lower[27–30] and higher incidences.[9,10] Our data on E2A–PBX1 fusion incidence are also comparable to the majority of Western and Chinese data.[12,13,16] The mean total leukocyte count in this subgroup was significantly high compared with the overall mean. All attained MRD negativity at the end of induction. Although E2A–PBX1 fusion is known to have a higher incidence of late CNS relapse, it has good outcomes and does not warrant intensive therapy in the absence of other high-risk prognosticators.[31]

The incidence of BCR-ABL translocation in our study (3%) is comparable to that of the reports from Western data, but

Table 3 Comparison of numerical chromosome abnormalities of various studies

Country	Author	Number of children with B-ALL	Hyperdiploidy, *n* (%)	Hypodiploidy, *n* (%)
India	Our study	98	7/83 (8.4)	1/83 (1.2)
India	Bhandari et al[9]	143	15 (10.5)	22 (15.4)
India	Mazloumi et al[10]	70	7 (10)	0
India	Amare et al[22]	78	12 (15)	30 (38.4)
Iran	Safaei et al[11]	88	28 (31.8)	4 (4.4)
China	Chen et al[13]	726	77 (10.6)	0
Argentina	Alonso et al[17]	326	63 (20)	6 (1.8)
Britain	Moorman et al[12]	1725	562 (38)	18 (1)
France	De Braekeleer et al[14]	93	37 (39)	4 (4.3)
Brazil	Mesquita et al[18]	88	11 (12.5)	4 (4.5)
Nicaragua	Ceppi et al[19]	64	16 (25)	0
Costa Rica	Santamaría-Quesada et al[20]	65	15 (23)	1 (1.15)
Britain	Hann et al[15]	1658	566 (34)	109 (6.5)
The USA	Gaynon et al[16]	1946	494 (25.4)	114 (5.8)

Abbreviation: ALL, acute lymphoblastic leukemia.

majority of the Indian data have reported higher incidences, ranging from 5% to 15% (►Tables 4 and 5). The mean age of children with BCR-ABL was similar to the overall mean age, although historically this fusion transcript is associated with older age group. The mean total counts were significantly high compared with the overall mean, which agrees with the reported literature.[32] All were treated with imatinib along with a backbone of four-drug induction and achieved morphological remission and MRD negativity at the end of induction.

MLL–AF4 fusion was identified in one child, with incidence (1%) comparable to the majority of Indian and Western data (►Tables 4 and 5). The low incidence of MLL rearrangement in children compared with infants (80%) is well-known. However, a few Indian studies have reported higher incidences, ranging from 6.3 to 10%.[10,25] While both infants and adults with the t(4;11)(q21;q23) are at high risk of treatment failure, children with the t(4;11)(q21;q23) appear to have a better outcome than either infants or adults.[33] In our study, the child with t(4;11) was otherwise National Cancer Institute (NCI) standard risk, received high-risk induction, and attained BM remission and MRD negativity at the end of induction.

Cytogenetics and molecular genetics, although recognized as major prognosticators with respect to long-term outcomes in children with ALL, did not have a significant similar impact on end-of-induction MRD outcomes in our study. This probably illustrates that MRD outcomes are independent of chromosomal aberrations, although larger studies are required.

Limitations of the Study

The main drawback of our study is that it is a retrospective study. Cytogenetics data were not available for all children,

Table 4 Comparison of incidences of various chromosomal translocations with reports from outside India

Country	Author	Number of children with B-ALL	TEL-AML, *n* (%)	BCR-ABL, *n* (%)	E2A-PBX1, *n* (%)	MLLAF4, *n* (%)
India	Our study	98	12 (12.24)	3 (3)	5 (5)	1 (1)
China	Chen et al[13]	726	83/541 (15.3)	106 (14.6)	39 (5.3)	20 (2.7)
Argentina	Alonso et al[17]	326	18 (7)	14 (5)	18 (7)	0 (0)
Britain	Moorman et al[12]	1725	368 (25)	43 (3)	50 (4)	17 (0.98)
France	De Braekeleer et al[14]	93	13 (14)	4 (4.3)	6 (6.3)	2 (2.1)
Brazil	Mesquita et al[18]	88	21.21	3.03	9.68	0
Britain	Hann et al[15]	1658	128/659 (19.4)	25 (1.5)	47 (2.8)	15 (0.9)
US	Gaynon et al[16]	1946	95/504 (18.8	44 (2.3	67 (3.4	42 (2.2)

Abbreviation: ALL, acute lymphoblastic leukemia.

Table 5 Comparison of incidences of various chromosomal translocations with reports from outside India

Institute	Author	Number of children with B-ALL	Percentage of abnormal molecular transcripts	Method of analysis	Detected/total, *n* (%)			
					TEL-AML	BCR-ABL	E2A-PBX1	MLL-AF4
KKCTH, Chennai		98	21.4	Multiplex RT-PCR	12/98 (12.24)	3/98 (3)	5/98 (5)	1/98 (1)
TMH, Mumbai, AIIMS, Delhi	Siraj et al[8]	259	19	Multiplex RT-PCR	18/259 (7)	14/259 (5)	18/259 (7)	0/259 (0)
Jammu and Kashmir	Pandita et al[25]	40	50	Multiplex RT-PCR	8/40 (20)	6/40 (15)	2/40 (5)	4/40 (10)
KEM, Mumbai	Kerketta et al[27]	126	29	FISH	25 (27.8)	2 (2.2)	2 (2.2)	0
PGIMER, Chandigarh	Bhatia et al[28]	56	46.8	Multiplex RT-PCR	9/56 (16.07)	3/56 (5.35)	1/56 (1.79)	2/51 (3.5)
Kidwai Institute, Bengaluru	Mazloumi et al[10]	70	21.4 71.4 [a]	Karyotyping and FISH	1/23 (4.3)	6/70 (12.7)	5/70 (10.6)	3/70 (6.3)
AIIMS, Delhi	Sazawal et al[26]	35	8.5	RT-PCR	0/35 (0)	1/35 (2.85)	2/35 (5.7)	0/35 (0)
SRL, Mumbai	Bhandari et al[9]	143	56.6	Multiplex RT-PCR	8/143 (5.6)	13/143 (9.1)	13/143 (9.1)	5/143 (3.5)
North India	Fauzdar et al[29]	77	23.37 55.8 [a]		9/21 (42)	9/77 (11)	0	0
Kerala	Hill et al[30]	42	4.7	Multiplex RT-PCR	2/42 (4.7)	–	0	0

Abbreviations: ALL, acute lymphoblastic leukemia; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase polymerase chain reaction.
[a]Total percentage of abnormal karyotypes.

mainly due to sampling and processing constraints. Failure to identify chromosomal rearrangements cytogenetically in our study may be attributed (a) to the presence of low levels of nondividing leukemic cells (containing the chromosomal rearrangements) in the sample and (b) to the more sensitive RT-PCR.

Conclusion

Although several molecular cytogenetic techniques detect chromosomal aberrations, conventional karyotyping and molecular methods complement each other. RT-PCR can determine rearrangements independent of cell division and determine cryptic aberrations such as t(12;21) not identified with conventional karyotyping. TEL-AML was the most common fusion gene detected, while hyperdiploidy was the most common abnormality on conventional karyotyping. Nearly 53% of the patients had normal cytogenetic profile, out of which 88% were MRD-negative. Although 25% of children with TEL-AML had MRD positivity, larger studies are required to validate the same. End-of-induction MRD outcomes were independent of the presence of either favorable or unfavorable cytogenetics.

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Conflicts of Interest
None declared.

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