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Clinico-epidemiological features and response in childhood acute lymphoblastic leukemia at regional cancer center of Northeast India

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) comprises 19.3% of all childhood cancers in Northeast India. **Methods:** We analyzed clinicoepidemiological features and early response to the treatment of all the cases of childhood ALL (age <15 years) diagnosed and treated at Dr. B Borooah Cancer Institute over 1 year. **Results:** Of 52 eligible cases, 69% were male (male:female ratio of 2.2:1) and the mean age was 7.1 years. Thirty-three children (63%) had baseline white blood cell count ≥20 × 10^9/L. Precursor B-cell was most the common subtype seen in 61% of children. Seven cases (14%) had high-risk (HR) cytogenetics, with *t* (9,22) being the most common one. Male sex and HR cytogenetics were significantly associated with poor early responses. **Conclusion:** ALL is a common childhood malignancy with high cure rates. However, poor socioeconomic status and the presence of higher proportions of disease-related factors lead to poor outcome in this part of the country.

Key words: Cytogenetics, early response, minimum residual disease, risk stratification

Introduction

Leukemia constitutes about 30%–50% of all childhood cancers globally.[1-4] In India, the proportion of children with acute leukemia ranged from 26.7% to 52.3% of all childhood cancers.[5-7] However, in Northeast India, acute leukemia constitutes around 27% of all childhood cancers with acute lymphoblastic leukemia (ALL) being the most common, comprising 19.3% of all childhood cancers.[8]

We sought to provide a comprehensive assessment of clinicoepidemiological features and early response to the treatment of childhood ALL diagnosed and treated at our institute over a period of 1 year.

Methods

In this retrospective study, we analyzed all the cases of childhood ALL diagnosed and treated at Dr. B Borooah Cancer Institute, Guwahati, from January 1, 2018, to December 31, 2018. The study received the Institutional Ethics Committee approval.

All newly diagnosed children aged <15 years with flow cytometry-based diagnosed cases of ALL were included in the study. Children with relapsed ALL at presentation, referred patients from other centers for continuing part of their treatment, patients not received any treatment after confirmation of the diagnosis, and patients who failed to undergo complete diagnostic workup were excluded from the study. Clinicoepidemiological and treatment-related data were collected from patient case file and health records available in the hospital database.

Patients were risk stratified into standard risk (SR), intermediate risk (IR), and high risk (HR) ("SR:" defined as prednisolone good response [PGR], age 1 year to younger than 6 years, initial white blood cell [WBC] <20 × 10^9/L and M1 [<5% blasts] or M2 [≥5% to <25% blasts] marrow on day-15, and M1 marrow on day-33 [all criteria must be fulfilled]; "IR:" defined as PGR, age younger than 1 year or age 6 years or older and/or WBC ≥20 × 10^9/L and M1 or M2 marrow on day-15 and M1 marrow on day-33, or SR criteria but M3 [≥25% blasts] marrow on day-15 and M1 marrow on day-33; and "HR:" defined as at least one of the following – prednisolone poor response, IR and M3 marrow on day-15, M2 or M3 marrow on day-33, t(9;22) [BCR-ABL], or *t*(4;11) [MLL-AF4]).[9] All patients received initial treatment as per "SR" BFM 2002 protocol irrespective of the presence of baseline risk factors.

Day-8 hemogram after steroid use was used to evaluate early response ("*Good response*" was defined as absolute blast count <1000/mm^3 in peripheral blood).[9] After the completion of induction Phase I therapy, day-33 bone marrow blast percentage was used to define "minimum residual disease" (MRD) status (negative MRD defined as blast percentage <0.01% in bone marrow aspiration specimen by flow cytometry).[9] Early response to treatment includes both day-8 response and day-33 MRD. Treatment is intensified to "HR" protocol in patients who have not achieved negative MRD even after completion of both the induction phases of therapy. Early death was defined as death within 30 days of starting the treatment.

Results

A total of 73 patients of childhood ALL were registered at our institute during the study period. Of the 73 cases, 52 children were found to be eligible for inclusion in this study.

Patient profile

These included 36 (69%) boys and 16 (31%) girls, with male-to-female ratio was 2.2:1. The mean age for the entire cohort was 7.1 years (standard deviation [SD] ±4.7; percentile [1–3]–[3.1–11]).

Disease profile

Of the 52 patients of childhood ALL, precursor B-cell ALL was the most common subtype accounting for 32 (61%), B-cell type 11 (21%), and T-cell 9 (18%) of all cases [Table 1]. The most common presenting symptom was fever followed by bleeding and generalized weakness, which were present in 77%, 38%, and 26% of all patients, respectively.

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Regarding baseline hemogram, mean hemoglobin level was 6.9 g/dl (SD ±2.6; percentile [1-3]–[5–8.8]), mean WBC count was 110 × 10^9/L (SD ± 150 × 10^9/L; percentile [1–3]–[6022–161,500]), and mean platelet count was 52.8 × 10^9/L (SD ± 36.5 × 10^9/L; percentile [1–3]–[19,250–68,750]).

Of the 52 patients, cytogenetic profile was available for 49 patients. Normal cytogenetics was seen in 39 (80%) patients. Seven (14%) patients had HR cytogenetics (t[9,22] in 3 [43%]; *t*[4,11] in 2 [29%]; and *t*[1,19] and hypoploidy in 1 case [14%] each). Three (6%) patients had good risk cytogenetics (hyperploidy in two patients and t (12,21) in one patient). Cytogenetics report could not be retrieved for three patients [Table 1]. Baseline cerebrospinal fluid (CSF) cytology was performed in 49 of 52 children and was negative in all cases. CSF cytology was not done in three patients at baseline (low platelet count <10 × 10^9/L).

Table 1: Baseline demographic profile

Variables	*n* (%)
Age (years) (*n*=52)	
<1 and >5	27 (52)
1-5	25 (48)
Sex (*n*=52)	
Male	36 (69)
Female	16 (31)
Subtype (*n*=52)	
Precursor B-cell	32 (61)
B-cell	11 (21)
T-cell	9 (18)
Hb, g/dl (*n*=52)	
<10	44 (85)
≥10	8 (15)
WBC count, ×10^9/L (*n*=52)	
<20	19 (37)
≥20	33 (63)
Platelet count, ×10^9/L (*n*=52)	
<100	42 (81)
≥100	10 (19)
Cytogenetics (*n*=49)	
HR	7 (14)
Normal	39 (80)
Good risk	3 (6)

HR=High risk, Hb=Hemoglobin, WBC=White blood cell

Treatment response

Early deaths were seen in 11 (21%) of 52 children. The most common cause was bleeding which accounts for early death in 7 cases (64%) and tumor lysis syndrome and febrile neutropenia in 2 cases (18%) each. Mean number of days from start of treatment to early deaths was 5.5 days (range 3–13 days).

Early response to treatment was assessed with day-8 peripheral blood blast count in 45 of 52 patients (seven children died before completing day-8 steroid) and day-33 MRD assessed in 41 of 52 patient (11 children died before completing Phase I of induction chemotherapy). Of 45 children, 8 (18%) children did not achieve "good response" to steroid and 11 (27%) children had positive MRD after completing Phase I induction therapy [Table 2].

On further analysis, it was found that male sex had poor early responses (poor day-8 response in 8 patients [26%] [*P* = 0.04; confidence interval (CI) 95%] and positive day-33 MRD in 11 [39%] patients [*P* = 0.007; CI 95%]) [Table 2]. The presence of HR cytogenetics was also found to be associated with poor day-8 response in 4 (57%) patients (*P* = 0.01; CI 95%) and positive day-33 MRD in 4 (66%) patients (*P* = 0.04; CI 95%). Contrary to this, age <1 and >5 years and higher baseline WBC counts ≥20 × 10^9/L were not seen to be significantly associated with poor early responses. Regarding subtypes of ALL, although precursor B-cell and T-cell ALL were found to have better day-8 response as compared to B-cell type; however, the association was not found to be statistically significant (*P* = 0.07; CI 95%).

Discussion

In this study, we found the mean age of children with ALL to be 7.1 years with male preponderance. The proportion of

Table 2: Factors associated with poor early responses

Variables	Poor early response			
	Day-8 peripheral blood blast count ≥1000/mm³ (*n*=8/45)	*P*	Day-33 MRD (bone marrow blast ≥0.01%) (*n*=11/41)	*P*
Age (years)				
<1 and >5	2	0.17	4	0.43
1-5	6		7	
Sex				
Male	8	0.03	11	0.008
Female	0		0	
WBC count, ×10^9/L				
≥20	7	0.08	9	0.09
<20	1		2	
Subtype				
Precursor B-cell	3	0.07	8	0.83
B-cell	4		2	
T-cell	1		1	
Cytogenetics				
HR	4	0.01	4	0.04
Normal	4		7	
Good risk	0		0	

MRD=Minimum residual disease, HR=High risk, WBC=White blood cell

children with baseline WBC count ≥20 × 10^9/L was 33 (63%). Precursor B-cell was the most common subtype and children with T-cell subtype were 7 (18%) of all cases. Seven (14%) of 49 cases had HR cytogenetics, of which *t*(9,22) was most commonly present in 3 (43%) of seven children. The number of early deaths was 11 (21%), of which bleeding was the most common cause. Regarding early response to treatment, 8 (18%) of all evaluable children had poor day-8 response to steroids and 11 (27%) children had positive day-33 MRD. Male sex and HR cytogenetics were significantly associated with poor early responses. B-cell subtype was associated with poor early responses as compared to precursor B-cell and T-cell subtype, but the difference was not statistically significant.

Age at presentation and male sex predominance in our study were found to be similar when we compared the results with other Indian studies.[10-12] The proportion of T-cell subtype was lower (18% in our study) than average of 30%–50% in different Indian studies.[10,13] More children presented with higher baseline WBC count (65% in our study) than average of 30%–40% in other studies.[10,14,15] We found higher proportions of BCR-ABL positivity (43% vs. 8.3% from a South Indian study).[16] We did not found any CNS-positive disease at baseline, as compared to 3%–6% positivity reported in various Indian studies.[12,17,18] We also found higher early deaths in our study (21% vs. 10%–12%) compared to other studies from India.[17,18] Regarding early treatment response rates, we found negative day-33 MRD as 73% when compared with morphological complete response (CR) of 83%–94% reported by different studies from India.[10,17-19] It is inappropriate to compare day-33 MRD with morphologic CR, as bone marrow assessment for MRD was not done in majority of those studies which were conducted before the year 2010. Reason for poor early response seen in our study is due to higher proportion of children with HR factors.

Poor outcomes of treatment in middle- to low-income countries are mainly attributed to frequent treatment abandonment, more early toxic deaths, and higher relapse rates as compared to high income countries.[8,20]

Conclusion

ALL is a common childhood malignancy with high cure rates. However, poor socioeconomic status in addition to the presence of higher proportions of disease-related risk factors in children with ALL leads to poor outcome in this part of the country.

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Conflicts of interest

There are no conflicts of interest.

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