

Profile of Acute Lymphoblastic Leukemia in Children Under 2 Years of Age

Abstract

Context: Acute lymphoblastic leukemia (ALL) shows substantial differences in clinical and laboratory features and treatment responsiveness in different subgroups. Pediatric ALL <2 years is associated with worse outcome. Infantile ALL is characterized by high white blood cell (WBC) counts, bulky extramedullary disease, translocations of 11q23 locus. There is paucity of data on ALL under 2 years of age. **Aims:** This study aims to analyze clinical, hematological, biochemical, immunophenotypical parameters, and treatment responsiveness of ALL under 2 years. **Settings and Designs:** It is a retrospective data analysis conducted at a Tertiary Care Cancer Centre in South India. The study population includes all pediatric ALL, registered at this institute during January 2009 to December 2013, who were under 2 years at the time of presentation. **Materials and Methods:** There were 122 cases of ALL under 2 years of age of whom 48 refused treatment, and four were lost to follow-up. Thus, 70 cases are eligible for analysis. Details on clinical, hematological, biochemical, radiological, immunophenotypical, and cytogenetic features were collected from case records, hospital cancer registry, and analysis done using SPSS version 20. Kaplan–Meier curves plotted for survival analysis. **Results:** Male:female ratio was 1.26:1 (infants - 1:1; 1–2 years group - 1.3:1). The most common clinical features were hepatomegaly (95%) and fever (89%). Hemoglobin level >11 gm% was seen in 12%, WBC counts above 50,000 in 26% and platelets below 20,000 in 20%. Elevated lactate dehydrogenase presents in 64% and uric acid in 12%. Immunophenotype done in 44 children; precursor-B ALL-41, precursor-T ALL-3. Central nervous system -positive disease and 11q23 translocation were noted in one infant each. **Conclusions:** Infants with ALL are associated with poor prognosis. Children in the 1–2 years are associated with significantly better outcome. WBC counts >50,000 are associated with poor prognosis among infants. Treatment refusal/abandonment rate is 43% in the study population which is comparable to that in literature.

Keywords: Acute lymphoblastic leukemia, infantile, prognosis, survival

Introduction

Acute lymphoblastic leukemia (ALL) is hallmarked by heterogeneous characteristics and treatment responsiveness in different subtypes. Although the overall cure rate of ALL has improved significantly over the past few decades, cure rates for specific ALL subgroups show marked variation.^[1-7] Age at diagnosis is identified as an important prognostic marker of pediatric ALL.^[8] It has been recognized that children with ALL, <2 years of age, tend to have a worse outcome as compared to older children and those under 1 year particularly do badly.^[9-12] Approximately 2.5%–5% of ALL are infantile and is associated with increased incidence of high white blood cell (WBC) counts, bulky extramedullary disease, translocations of MLL gene at

chromosome 11q23.^[9-22] This study aims at analyzing clinical, hematological, biochemical, immunophenotypical parameters, and treatment responsiveness in children under 2 years of age, who are diagnosed with ALL.

Materials and Methods

It is a retrospective data analysis conducted at a Tertiary Care Cancer Centre in South India. The study population includes all Pediatric ALL, registered at this institute from January 2009 to December 2013, who were under 2 years at the time of presentation. The details included in the study were collected from case records, hospital cancer registry, and during follow-up.

The total number of pediatric malignancies registered during the period

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were 2640, of whom 422 cases were under 2 years of age with ALL contributing 122 cases (29%). Among them, 48 children refused treatment due to various reasons, and four were lost to follow-up. Thus, 70 children are eligible for analysis. Common clinical features such as fever, pallor, lymph node enlargement, hepatomegaly, splenomegaly, and bleeding were noted in each patient. Hemoglobin (Hb) levels were classified into three groups such as <7 gm%, 7–11 gm%, >11 gm%; WBC counts into <10000, 10,000–49,000, and >50,000; platelet counts into <20,000, 20,000–99,999, and >1 lakh. The upper limit of lactate dehydrogenase (LDH) was taken as 240 U/l and that of uric acid 6 mg%. CSF study was done to look for central nervous system (CNS) involvement.

The diagnosis of ALL was based on morphological, cytochemical, and immunohistochemical features. Lymphoblasts were classified into L1, L2, or L3 based on their morphology in Wright-Giemsa stained bone marrow smears. Cytochemistry looked into blasts positive for terminal deoxynucleotidyl transferase, periodic acid–Schiff, and negative for myeloperoxidase. Immunophenotype was identified as B-cell ALL when there are at least 20% (log2) cells positive for CD19 and CD24 and negative for CD2, CD5, and CD7. Similarly, T-cell phenotype was confirmed when at least 20% (log2) cells are positive for CD2, CD5, and CD7.

The treatment protocol followed was MCP 841 consisting of induction, intense consolidation (I₂A), re-induction, conventional consolidation, and maintenance. The dose of each drug used was vincristine-1.4 mg/m², daunomycin (30 mg/m²), L-Asparaginase (6000U/m²), Prednisolone (40 mg/m²), high-dose Ara-C (2 g/m²), cyclophosphamide (750 mg/m²), 6-MP (75 mg/m²), and oral Methotrexate (15 mg/m²), respectively. Infants below 1 year were given 50% of the dose. All infants received triple IT irrespective of CNS disease status. The dose of intrathecal methotrexate was 6 mg for infants below 1 year and 8 mg for 1–2 years and that of Ara-C was 20 mg for infants and 30 mg for 1–2 years. BM examinations were done at the end of every cycle with additional CSF study after consolidation and each maintenance cycle. Follow-up was done every month in the 1st year after completion of therapy, every 2 months in the 2nd year, three monthly in the 3rd year and yearly thereafter.

The clinical, hematological, and molecular variables collected were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY). The primary outcome measured was event-free survival (EFS), starting from the date of registration. The various events considered for calculating EFS were (i) induction failure (failure to achieve remission or induction death), (ii) leukemic relapse at any site, (iii) death, and (iv) second malignancy, whichever occurred first. Kaplan–Meier curves were plotted for both age groups.

Results

Among the 70 children, infants were 12 (17%) and the remaining 58 (83%) were in the 1–2 years group. There were 39 males (56%) and 31 (44%) females, the ratio being 1.26:1. In the infants' group, there were equal number of males and females whereas males were more (1.3:1) in the 1–2 years' group. The most common clinical features were hepatomegaly, noticed in 66 children (95%) followed by fever in 62 children (89%). Other common features were pallor and splenomegaly in 57 (81.5%) each, lymphadenopathy in 52 (74%), bleeding in 9 (11.5%), and parotidomegaly in 3 (4%) [Table 1].

Hemogram revealed Hb <7 gm% in 23 children (33%), 7–11 gm% in 39 children (55.5%), and >11 gm% in 8 children (11.5%). Initial WBC counts were <10,000 in 27 (38%), between 10,000 and 49,000 in 25 (36%), and 18 (26%) had >50,000 counts. The platelet counts were <20,000 in 14 children (20%), 20,000–99,999 in 52 (74.5%), and above 1 lakh in 4 (5.5%).

Serum LDH was elevated (>250 IU) in 45 children (64%) and Uric acid (6 mg/dL) in 8 (11.5%). Renomegaly was detected by ultrasound in 13 (18.5%). Only one infant

Table 1: Clinical and laboratory features

Variable	Total (%)	<1 year (%)	1-2 years (%)
Fever	89	92	88
Pallor	81.5	83	81
Lymphadenopathy	74	33	82
Bleeding	11.5	8	14
Hepatomegaly	95	92	96
Splenomegaly	81.5	58	86
Renomegaly	18.5	33	15
Hb			
<7	33	33	33
7-11	55	50	57
>11	12	17	10
TC			
<10,000	38	17	43
10,000-49,000	36	42	35
>50,000	26	41	22
Platelets			
<20,000	20	17	21
20,000-99,999	74.5	83	72
>100,000	5.5	0	7
Morphology			
L1	30	42	27
L1/L2	64	58	66
L2	6	0	7
IPT			
B-cell	93	83	95
T-cell	7	17	5
CNS positive: 1 case (1.4%)		8.3	0
11q23 mutation: 1 case (1.4%)		8.3	0

Hb – Hemoglobin; CNS – Central nervous system; TC – Total WBC Count; IPT – Immunophenotype

had CNS-3 disease at presentation, and nobody was CNS positive in the 1–2 group. L1 morphology was seen in 21 children (30%), L1/L2 in 45 (64%), and L2 in 4 (6%). Immunophenotype was done in 44 children, of whom 41 (93%) were precursor B-ALL and 3 (7%) precursor T-ALL. 11q23 translocation was detected in one infant.

Estimated 5-year EFS was 61.4% for the whole cohort. The 5-year EFS for infants under 1 year was 33% and that for 1–2 years 67% [Figure 1]. The difference in EFS between the two groups is statistically significant ($P = 0.009$). Among those who had $>50,000$ WBC counts, none of the five infants survived, whereas 8/13 in the 1–2 group are alive without any events. All three children with precursor T-ALL survived [Table 2].

Table 2 shows the frequency of various events considered for the calculation of survival in each group separately. In the first group, six infants (50%) succumbed during induction, whereas there were only three induction deaths (5%) in the second group, the cumulative incidence being 12.8%. There was only one relapse (BM) in the first group (8%) when compared to the 12 relapses (19%) in the second group, of whom 11 were in the BM and one in the testis. Among the total of 13 relapses, 10 were early BM relapses, and three were late (one testicular and two BM). The number of children who died in remission while on

therapy were 1 (8%) and 5 (9%) in the first and second groups, respectively. Five of them died due to septicemia and one due to intracranial hemorrhage. Only one child failed to achieve remission after induction [Figure 1].

Discussion

The incidence of organ involvement is higher in our series when compared to that in older children, with hepatomegaly being the most common (95%).^[8] This observation tallies with the fact that infants and younger children who have got increased incidence of organ involvement. There is a higher proportion of children with WBC counts $>50,000$ as is expected in this age group. Initial WBC counts being an independent prognostic marker, this may be one of the reasons that contribute to poor prognosis of infants and young children with ALL. In our series, 18 children had a WBC count $>50,000$. Among them, all of the 5 infants and 5 out of the 13 in the second group succumbed, showing its clear association with dismal outcome. Although we could not establish a statistically significant difference between the survival of those with $>50,000$ WBC counts and those with less counts ($P = 0.076$), the Kaplan–Meier survival curves show that the difference in survival between the two groups is substantial [Figure 2].

Several older studies have mentioned age below 2 years as an independent prognostic marker.^[9–11] Later, it was shown that the dismal prognosis is mainly associated with age <1 year, whereas those in the 1–2 years of age have survival comparable to older children.^[9] The results obtained in our study are in line with this observation. The survival we observed in the infants' group is 33% which is consistent with that of many other studies. Although precursor T-cell ALL has a worse outcome as compared to precursor B-cell disease, our study failed to establish a significant difference between these groups.^[8] This may be partly attributed to the smaller number of cases of precursor T-cell ALL.

Table 2: Treatment outcome

Relapse	<1 year (n=12)	1-2 years (n=58)
BM	1 (early-1)	11 (early-9; late-2)
Testes	0	1 (late)
CNS	0	0
No remission	0	1
Induction death	6	3
Death in remission	1 (sepsis)	5 (sepsis-4; IC bleed-1)
Survivors	4	37

BM – Bone marrow; CNS – Central nervous system; IC – Intra Cranial

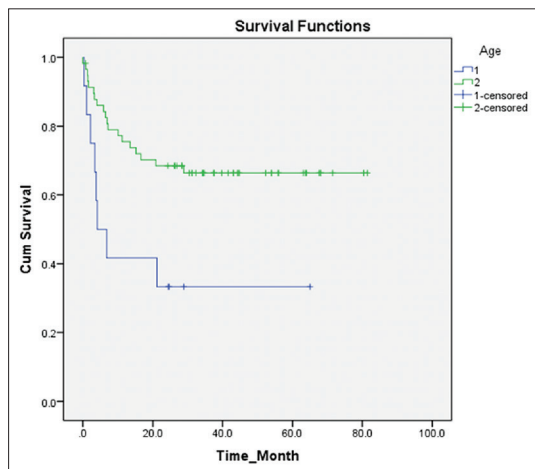


Figure 1: Comparison between the 5 years' event-free survival of children in two different age groups 1: Age <1 year; 2: Age 1–2 years

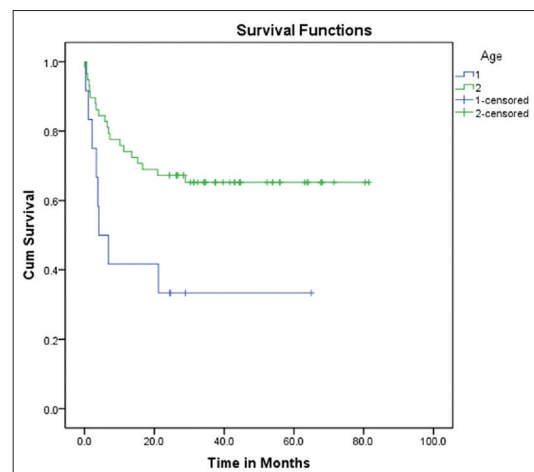


Figure 2: Comparison between the 5 years' event-free survival of children with initial white blood cell counts below and above 50,000. 1: white blood cell $>50,000$; 2: white blood cell $<50,000$

Contrary to the belief that, the frequency of CNS-positive disease is high in the infantile ALL, we got only one case positive for CNS disease. These differences may be explained by the geographical and biological differences among the study population, as the published data are mainly from the West.

The poor prognosis associated with infantile ALL may be attributed to unique features such as high leukocyte count, increased incidence of CNS disease, massive organomegaly, CD 10 negativity, MLL gene rearrangement and vulnerability to complications and toxicities. There are very limited data to guide how the distinct physiology of infants (in terms of body composition, binding of drugs to plasma proteins, cytochrome p450 activity, renal function, and immunocompetence) should be considered in designing chemotherapy treatment protocols.^[15] Initial protocols for the treatment of infant ALL have encountered problems with the excessive level of toxicities. Later, they were modified in such a way to reduce the toxicity profile and thereby the mortality.^[23-26]

Considering the dismal prognosis on current intensive therapies, novel therapeutic approaches, including stem cell transplantation, immunotherapy with anti-CD19 agents and FLT3 tyrosine kinase inhibitor should be incorporated into the treatment of ALL in infants along with high-quality supportive care.^[15,27-29]

Conclusions

Infants with ALL are associated with poor prognosis. Children in the 1–2 years are associated with significantly better outcome. WBC counts >50,000 are associated with poor prognosis among infants. Treatment refusal/abandonment rate is 43% in the study population which is comparable to that in literature.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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