Original Article

Prognostic Factors of Acute Lymphoblastic Leukeamia in Children

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Objective To look into the known prognostic factors of Acute Lymphoblastic Leukeamia in Children

Materials and Methods: A retrospective study on children with a diagnosis of acute lymphoblastic leukeamia was conducted at Oncology department, Children Hospital, Pakistan Institute of Medical Sciences Islamabad. All the Leukaemic patients registered form January 2007- August 2009 were included in this study. Their detailed clinical history specially age, sex, lymphadenopathy, hepatosplenomegaly, testicular enlargement, mediastinal masses as well as the CNS disease was thoroughly interrogated. All pre-induction investigations including Haemoglobin level, white blood cell Count, Platelet count, peripheral blast count and bone marrow blast count were noted and compared with the post induction values.

Results: Among the children having acute lymphoblastic leukeamia the mean age of presentation was 5 years four month with male to female ratio of 2:1. 58% of patients had hepatomegaly and 60 % had splenomegaly. Pre-induction bone marrow blast count in majority of the patients was $\geq$80%. Pre-induction mean WBC count was 26.3 x 10^9, mean Hb was 7.1 g/dl, and mean platelet count was 77.1 x 10^9. The post-induction WBC count was 3.5 x 10^9, mean Hb was 8.9 g/dl and platelet count was 174.2 x 10^9. Regarding the FAB classification, 60% of the cases were of ALL-L1; these patients showed a good response in 86% and were categorized prognostically as M1 [on post- induction blast count basis].

Conclusions: Majority of children with ALL had ALL-L1 morphology, having pre-induction bone marrow blast cell count of >80%, which reduced to <1% with multi-agent induction therapy.

Key words: Acute Lymphoblastic Leukeamia, Prognostic Factors, Hepatosplenomegaly, Peripheral blast count, Prednisolone response

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children, representing nearly one third of all pediatric cancers. The annual incidence rate for acute lymphoblastic leukemia is 30.9 cases per million population. The peak incidence occurs in children aged 2-5 years.[1]

This disease has been recognized as clinically and morphologically heterogeneous. Morphologically it has been classified according to the FAB (French, American and British) criteria into three subtypes, L1, L2 and L3.[2-4] This system of classification, which is still valid, had been proven to be clinically reproducible.[1-3]

The current study is planned to verify the incidence of ALL subtypes and their relation to age, sex and clinical and haematological presentations along with response to therapy in our setup. ALL in infancy has been associated with unfavorable features such as hyperleukocytosis, hepatosplenomegaly, and central nervous system (CNS) disease.[4, 5] Correlation between various clinical and laboratory characteristics and outcomes has been studied. These factors are interrelated, making it difficult to identify independent prognostic factors. Higher white blood cell (WBC) count correlates with worse outcomes, but the WBC categories for comparison have varied in the different reports.[6-8] In the last 30 years, the cure rate in Childhood acute lymphoblastic leukemia (ALL) has increased to 80%.[9] Remission induction therapy generally consists of a combination of three or four drugs (vincristine, prednisone, and L-asparaginase, with or without an anthracycline) with CNS prophylaxis, based on the risk classification at diagnosis. This multi-agent therapy achieves complete remission (CR) in the vast majority (> 95%) of children with ALL.[10-14]

Table I: Baseline characteristics of the study patients (n 50)

	Number	%
Age (years)		
Mean ± SD	5.4 ± 3.1	
Range (min – max)	2 – 12	
Age Distriution		
(years)	0	0
< 1	9	18
1 – 2	35	70
2 – 10	6	12
10 – 15		
Sex		
Male	33	66
Female	17	34
Male : Female Ratio	2 : 1	

Materials and Methods

A retrospective study on children with a diagnosis of ALL was conducted at Oncology department, Children Hospital, Pakistan Institute of Medical Sciences Islamabad. All the fifty newly diagnosed acute leukaemic patients registered form January 2007- August 2009 were included in this study.

A detailed history and physical examination were conducted, concentrating on the presence of the following: fever, pallor, bleeding tendency, lymphadenopathy, splenic or liver enlargement, neurological and testicular manifestation in males and any radiological evidence for the presence of mediastinal masses. The following haematological investigations were done: Hb concentration, WBC and platelet count using an automated hematology analyzer (Sysmex kx-21). Cytomorphological examination of bone marrow smear had been done.[8] The original FAB criteria and the FAB scoring system were used to differentiate between L1 and L2 morphological subtypes.

Statistical analysis: A statistical survey had been done including the percentage, mean and standard deviation on SPSS version 14.

Results

In this study a total of 50 patients were enrolled.

Age & Sex Distribution: In this study of 50 patients, the age ranged from 2–12 years with a mean of 5.4 years. Male gender was in dominance in the study with 66% presentation. Male to female ratio was 2: 1.Table I

Lymphadenopathy, Liver and Spleen status (Table 2): In 25 (50.0%) cases the palpable lymph nodes were > 3 cm and in remaining 25 (50.0%) < 3 cm in diameter. Out of total 50 cases, in 2 (4.0%) the liver was found mildly enlarged while in 27 (54.0%) it was moderately enlarged. As regards spleen, in 6 (12.0%) cases it was mildly enlarged; it was moderately enlarged in 24 (48.0%) cases while 1 patient had spleen was palpable beyond umbilicus.

Masses and other manifestations: It was found that in 3 (6.0%) cases the testicles had enlargement and only in 1 (2.0%) patient a mediastinal mass was found. None of the study patients had CNS disease.

Table II: Lymphadenopathy, Liver and Spleen status in study patients (n = 50)

	Number	%
Lymphadenopathy		
> 3 cm	25	50
< 3 cm	25	50
Liver		
Not palpable	21	42
Mild enlarged	2	4
Moderate enlarged	27	54
Markedly enlarged	0	0
Spleen		
Not palpable	1	2
Mild enlarged	19	38
Moderate enlarged	6	12
Markedly enlarged	24	48

Blast cells in peripheral blood (%): In a total 50 cases, 14 (28.0%) had percentage < 20 on peripheral film. Seven (14.0%) cases each had blast between 21% to 30% and 31 to 40%. Another 6 (12.0%) cases had blast between 41 and 51%, 7 (14.0%) had blast between 51 and 70% while 9 patients had blast of more than 70% on peripheral film.

Blast cells in the bone marrow smears: Majority of patient (60%) showed >80% blats in the bone marrow smears. In only 18%, these cells were ≤50%, and in the remaining 22% between 51 and 80%.

FAB Classification and bone marrow status: Thirty (60.0%) patients had FAB class of ALL-L1, 16 (32.0%) had ALL-L2 while in 4 (8.0%) cases the FAB class could not be determined. Similarly, majority 43 (86.0%) of the study patients had good response to prednisolone while only 7 (14.0%) had poor response. The distribution of bone marrow according to classes showed that majority 44 (88.0%) cases belonged to M1, 3 (6.0%) to M2 and 3 (6.0%) of the patients were from M3 class of bone marrow. Table III

Table III: FAB types, response to induction therapy and bone marrow status (n 50)

	Number	%
FAB class		
ALL-L1	30	60
ALL-L2	16	32
Not determined	4	8
Response to Induction therapy	6	12
Poor	44	88
Good		
Bone marrow status		
M1	44	88
M2	3	6
M3	3	6

Post induction bone marrow blasts: The majority of the cases 40 (80.0%) had < 1% bone marrow blast after induction therapy was completed. Amongst the remaining cases 2 (4.0%) had < 2% blast, 1 had bone marrow blast between 3 and 5 % while 7 (14.0%) patients had post induction blast of 5% or above.

Pre and post induction status of WBCs, Hb level and platelets, Table IV:

Table IV: Hematological findings pre and post induction (n 50)

Parameters	Pre-Induction Range Mean ± SD	Post-Induction Range Mean ± SD	p-value
WBCs ($x10^9$/l)	3.1 – 488 26.30 ± 76.22	2.5 – 12.5 3.54± 3.32	0.05
Hemoglobin	2.5 – 13.0 7.1 ± 2.4	3.8 – 11.4 8.9 ± 1.6	<0.001
Platelets	363 – 419 77.14± 98.1	4 – 634 174.3 ± 170.21	0.002

The average pre induction WBC was 26.31 x 10^9/l with range from 3.1 to 48.8 x 10^9 /l while the average post induction WBCs were 3.5 x 10^9/l with range from 2.5 to 12.5 x 10^9 /l. The difference between means was found statistically significant (p 0.05). The mean hemoglobin level pre-induction was 7.1 ranging from 2.5 to 13.0 while post induction mean hemoglobin was 8.9 ranging from 3.8 to 11.4. The difference between mean hemoglobin levels pre and post induction was found to be statistically highly significant (p<0.001). The mean platelets pre induction was 77.14 x 10^9 /l with range from 36.3 to 419 x 10^9 /l while post induction mean platelets were 174.29 with range from 4 to 634 x 10^9 /l. The difference between pre and post induction mean platelet counts was found to be statistically significant (p 0.002).

Discussion

There is considerable variation in risk classification of ALL used by the major clinical trial groups treating paediatric cancers. Since mature B cell ALL (FAB type ALL-L3) is treated differently from precursor B or T cell ALL (FAB type ALL-L1 or L2). For the most part, these systems for the treatment of B-precursor ALL (and sometimes T-cell ALL) are based on age and WBC at diagnosis, prognostic features which have consistently been found to be important.[15,16] In our study 70% of children presented were between the ages of 2-10 years while male to female ratio was 2:1. Mean pre-induction WBC count in our study was 26.300 x 10^9 /L.

In addition to the time-honored features of age and WBC, the presence of extramedullary disease (CNS or overt testicular involvement) is a factor used to determine the intensity of treatment. Overt CNS leukemia is more common in T-cell ALL than in B-precursor ALL[17], occurs in fewer than 5% of children at diagnosis, and is generally predictive of a poor treatment outcome.[18] However in our study none of the patients had CNS involvement that showed good response to therapy. Overt testicular involvement at diagnosis is even less common. A series from St. Jude reported the incidence to be 1.9% of boys[19], although occult testicular disease has been found by biopsy in as many as 25% of newly diagnosed boys.[20] In our study the testicular enlargement was 6%. Slow early response to induction has been defined in several ways: the presence of any circulating blasts following one week of multiagent induction[21], or greater than 25% blasts in the marrow on day 7 of induction.[22] All of these findings have been found to be important predictors of an adverse outcome, although intensified therapy appears to abrogate the prognostic significance of a slow early response.[23] Slow clearance of peripheral blasts has also been found to be an adverse prognostic feature in T-cell ALL and Ph+ ALL.[21, 24, 25] In our study 88% of the patients show good response to prednisolone and had bone marrow status of M1 (<5%) blasts. Only 6% were in stage M2 (blasts between 5-25%) and another 6% were in stage M3 (blasts >25%).

Conclusion

Most of the patients with ALL were between 2-10 years of age. the male to female ratio was 2:1. The lymphadenopathy and hepatosplenomegaly features were found in most patients. Majority of the children with ALL had ALL L1 morphology, having pre-induction bone marrow blast count of > 80% which reduced to < 1%

blast with multi agent induction therapy. The comparative hematological parameters like Hemoglobin, WBC count and Platelet count were also suggestive of improvement.

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