RESEARCH PAPER

Childhood T-lineage Acute Lymphoblastic Leukemia: Management and Outcome at a Tertiary Care Center in North India

LS ARYA, KS PADMANJALI, S SAZAWAL, R SAXENA, M BHARGAVA, KP KULKARNI, M ADDE AND I MAGRATH

From Department of Pediatrics, Division of Pediatric Oncology, All India Institute of Medical Sciences, New Delhi, India. Correspondence to: Dr LS Arya, Senior Consultant, Pediatric Oncology & Hematology, Apollo Center for Advanced Pediatrics, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi 110 076, India. lsarya@rediffmail.com
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Objective: To assess the clinical features, prognostic factors and outcome of childhood T-ALL in comparison with B-lineage ALL, treated with a uniform treatment regimen (MCP 841).

Setting: Pediatric oncology division of a tertiary care institution in Northern India.

Design: Retrospective analysis of clinical data and survival outcome.

Participants: 60 children with T-ALL and 139 with B-lineage ALL, and less than 15 years of age treated over 15 years.

Results: T-ALL was observed in 30%. High risk features at presentation (age ≥10 years, WBC >50,000/mm^3, mediastinal mass, and CNS leukemia) were significantly more frequent in T-ALL as compared to B-lineage ALL (P=0.049, P<0.001, P<0.001 and P=0.02, respectively). Fifty five of 60 T-ALL patients (91.7%) achieved complete remission after induction therapy. There were 3 induction and 10 remission deaths while 11 (18.3%) relapsed. The overall survival and event-free survival of T-lineage ALL (61.5±7.6 and 49.9±7.4, respectively) were similar to that of B-lineage patients (68.7±4.7 and 47.1±5.1, respectively). National Cancer Institute risk groups emerged as significant prognostic factor for event free survival only in B-lineage patients.

Conclusions: Even though high risk features were significantly more frequent in T-ALL, survival outcome was similar to that of B-lineage patients. None of the routinely described prognostic parameters significantly impacted survival.

Key words: *Acute lymphoblastic leukemia, B-lineage, Child, Prognosis, Relapse, Survival, Outcome, T-lineage*.

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T lineage acute lymphoblastic leukemia (T-ALL) is described to constitute about 15% of childhood ALL [1-4]. Authors from developing countries report it more frequently than in developed countries, possibly due to yet unidentified genetic and environmental factors [5-12].

Several studies conducted over the past two decades, from the developed countries have shown that the prognosis of T-ALL has improved significantly in the era of risk-adapted therapy with early intensification and timely and adequate CNS prophylaxis [13-17]. Majority of the study groups have stratified patients with T-ALL into a separate risk group for therapy and/or prognostication. Although this provides an excellent opportunity for evaluating unique contributions of prognostic factors within each immuno-phenotype group, direct comparison of outcome between T and B lineage becomes difficult because of the different treatment regimen used. Furthermore, there is paucity of data addressing clinical features, prognostic parameters and outcome of T-ALL in developing countries like India, where this ALL subtype is more frequently observed than in the developed nations [18,19].

In this communication, we attempt to determine the frequency, clinical features and outcome of patients with T-ALL in comparison with B lineage

ALL, treated on a uniform therapeutic regimen and to identify poor prognostic factors in T-ALL patients.

METHODS

Two hundred and fifty four children aged <15 years with newly diagnosed ALL received therapy in the Pediatric Oncology Division of the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi from June 1992 to June 2002. Diagnosis of ALL was confirmed by bone marrow examination at presentation. Cytochemistry using myeloperoxidase and sudan black was performed on all bone marrow aspirate/touch smear specimens.

For the purpose of evaluation, presence of one or more lymph node more than 1cm diameter was considered as lymphadenopathy; hepatomegaly was defined as liver palpable at least 2 cm below the costal margin and splenomegaly as palpable spleen. Presence of unequivocal blasts in the CSF at the time of presentation, irrespective of CSF cell count was considered as CNS leukemia.

Pre-treatment bone marrow or peripheral blood sample (of patients with WBC count >30,000/mm^3 with >75% blasts) were separated on Ficoll-Hypaque gradients and immunophenotyping was performed by using a panel of monoclonal antibodies (when sufficient sample was available), which included CD2,3,4,5,7,8,10,19,20,33,34, HLA-DR and surface immunoglobulin (SIg) by indirect immunoflourescence method. In cases where sample was insufficient, a minimum panel of monoclonal antibodies, which included CD3,5,7,10,19 and 33, were used.

T-ALL was defined as >20% blasts expressing at least 2 of the antigens CD2,3,5 and 7 or expressing only CD7 in the absence of B lineage and myeloid antigens; B-precursor was defined as CD19 positive, CD10 positive or negative and CD7 and 5 negative. T-ALL maturational stages were defined as pro-thymocyte leukemia (pro-TL) - $CD7^+$, $CD2^-$, 3^- and 5^-; Immature TL- $CD7^+$, $(CD2 \text{ or } 5)^+$ and $CD3^-$; Mature TL – $CD3^+$, and $(CD7, 2,5)^+$ [20].

Treatment: All patients were uniformly treated on MCP 841 protocol. CNS prophylaxis included intrathecal methotrexate given at weekly intervals for first 3 months and 1800cGy cranial irradiation for children more than 3 years. In lieu of irradiation, CNS prophylaxis in children less than 3 years of age consisted of triple intrathecal therapy with methotrexate, cytosine arabinoside and hydrocortisone, weekly during first 3 months of therapy and twice at monthly interval, during each maintenance cycle.

Evaluation of response: Bone marrow examination was performed at the end of induction therapy. Complete remission (CR) was defined as <5% lymphoblasts in a normocellular bone marrow with normal blood counts in the absence of clinical evidence of disease. Patients with blast percentage >5% at the end of induction were considered as non-responders. For purpose of evaluation, relapses were divided into on-therapy relapses occurring during the course of cancer chemotherapy and posttherapy relapses, occurring after completion of chemotherapy.

Statistical analysis: Data were retreived from hospital records and analyzed. The overall survival (OS), event free survival (EFS) and disease-free-survival (DFS) rates were calculated by the Kaplan-Meier method. OS was calculated from the date of commencement of treatment to the date of last follow-up. EFS was calculated from the date of commencement of treatment to the date of last follow-up or an event (induction death, induction failure, remission death or relapse). DFS was calculated for CR patients from the date of attainment of complete remission to the date of relapse or the date the patient was last known to be in complete remission. For the analysis of DFS, patients dying from causes other than relapse were censored at the time of death. Prognostic factors were analyzed with respect to their influence on outcome using the log-rank statistics and trend test for univariate analysis for both T and B lineage patients.

RESULTS

Immunophenotyping was performed in 199 (78.3%) of the 254 patients accrued in the study. Sixty of these had T lineage ALL. Their male to female ratio was 6.5:1 while mean age was 7.6 years (range 1-14 years) and the mean WBC count was 1,27,892/mm^3. 139 patients (70%) had B–lineage ALL. Male to female ratio in B–lineage ALL was 3.2:1; mean age of children with B–lineage ALL was 5.84 years (range: 1-14 years) and mean WBC count was 51,902 /mm^3.

When the clinical and laboratory parameters at presentation of patients with T-ALL were compared with those with B–lineage ALL, poor prognostic features like age >10 years, WBC count >50,000/mm^3, mediastinal lymphadenopathy and CNS leukemia were significantly more frequent in patients with T-ALL (***Table* I**). When patients were stratified in to risk groups based on NCI Consensus Group's age and WBC criteria [24], 68.3% of patients with T-lineage belong to the high risk group as compared to 36.7% of those with B-lineage ALL (P<0.005). Fifty five of 60 (91.7%) T-ALL patients attained CR after induction therapy. One patient was non responder while 3 and 10 patients died in induction and remission, respectively (as opposed to 19 and 16 induction and remission deaths, respectively in B-lineage patients). Infection and bleeding were the predominant causes of death in these patients (38.4%, 30.7%, respectively). Two patients were lost to follow up. Eleven of these 55 patients relapsed (20%), of which 5 (9.1%) relapsed on therapy and 6 (10.9%) relapsed after completion of the treatment. There were 8 (14.5%) bone marrow relapses, one each of CNS, bone marrow and CNS and extramedullary relapse.

The OS, EFS and DFS were 61.5±7.6, 49.9±7.4 and 71.3±7.9, respectively. There was no significant difference in OS and EFS in T and B lineage ALL (***Fig*. 1**). The T lineage and B lineage patients were stratified into standard and high risk groups based on National Cancer Institute (NCI), USA consensus group [15]. EFS was 35.9±12.0 for standard risk T-ALL and 55.4±6.4 for standard risk group with B lineage ALL. Although the trend of better survival in B lineage patients was in the expected direction the difference was not statistically significant (P=0.19) (***Fig.* 3**). On the contrary, EFS of T lineage patients in the high risk group was 57.9±8.1 as against 35.7± 8.1 for high risk patients with B lineage (P=0.005) (**Fig. 3**). The standard risk patients in B lineage group had a significantly favorable outcome than the high risk patients with B lineage ALL (P=0.02). In contrast, T lineage patients in high risk group had a better EFS than standard risk group patients, however the difference was not statistically significant (P=0.19)

We also stratified patients into different groups based on maturational stage of T lymphocyte. Majority of patients were in mature T cell group (53.3%) while a small subset belonged to pro-thymocyte group (8.3%). There was no significant difference in presenting clinical features and laboratory parameters with in the maturational stages of T cell (***Table* II**). Patients in the immature T cell group had a better EFS (61.4±10.8) compared to mature stage (50.2±9.6) even though the difference was not statistically significant (P=0.46). All 5 patients in Pro T-ALL group died during first few

TABLE I CLINICAL FEATURES OF T-ALL AND B-LINEAGE ALL

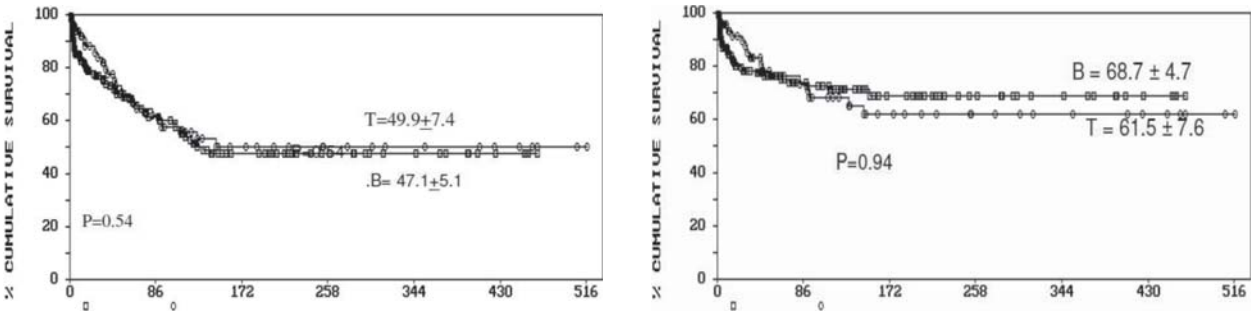
Clinical feature	T-ALL (n=60)(%)	B-lineage (n=139)(%)
Age <10 yrs‡	46 (77)	123 (88.5)
Male sex	52 (87)	106 (76)
Lymphadenopathy	54 (90)	117(84)
Mediastinal#	27 (45)	10 (7)
Hepatosplenomegaly	55 (91.6)	132 (95)
WBC <50,000/mm#	34 (57)	102 (73)
CNS leukemia‡	9 (15)	5 (3.5)
Low Risk*	19 (31.7)	88 (63.3)

*WBC: White blood cells; CNS: Central nervous system; *National Cancer Institute risk group; #P<0.001; ‡P<0.05: $P<0.005.*

TABLE II COMPARISON OF CLINICAL CHARACTERISTICS AND OUTCOME IN T-CELL MATURATIONAL STAGES

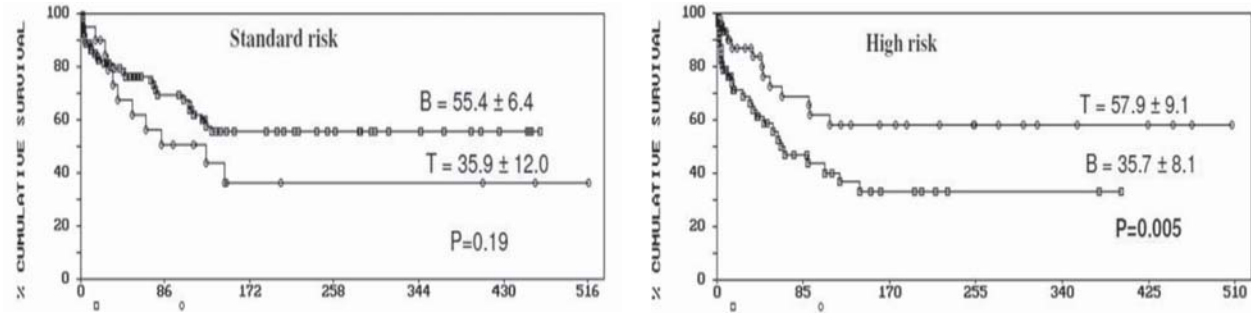
Characteristic	Pro T (n=5)	Immature T (n=23)	Mature T (n=32)	P value
Age				
<10 years	3	17	23	
≥10 years	2	6	9	0.82
WBC (×10^3/mm^3)				
<50	2	8	15	0.92
≥50 - ≤100	1	4	7	0.67
>100	2	11	10	0.46
Male sex	5	20	27	
Mediastinal lymphadenopathy	1	14	11	0.08
CNS leukemia	0	4	5	0.59
Relapse	1	4	7	0.89
EFS	0.00	61.4±10.8	50.2±9.6	0.46

EFS: Event free survival; WBC: White blood cell count.



(*a*) (*b*)

FIG. 1 *Event Free Survival (a) and overall survival (b) in T-ALL and B lineage ALL.*



(*a*) (*b*)

FIG. 2 *Event Free Survival in the study population according to NCI risk groups.*

months of therapy, cause of death being toxicity related events in 4 of 5 patients (80%).

On univariate analysis for EFS, none of the traditionally described prognostic factors like age, sex, WBC count, organomegaly, CNS leukemia and NCI consensus groups were significant for EFS in the T-ALL patients. In the B-lineage group, NCI consensus risk grouping was the only factor significant for prognosis ($P<0.05$).

DISCUSSION

According to this study, T-ALL was at least more than twice as frequent in our patient population (30%) as that in Western countries [1-4,13-17]. Frequency of T-ALL in our study (30%) was similar to studies from Tata Memorial Hospital (TMH) (21% in patients <21 years) and Cancer Institute, Chennai (46% in children <15 years) [9,18]. The high occurrence of T-ALL in our patients is probably related to the socio-demographic characteristics of the patient population. The majority of our patients belonged to the low socioeconomic group (58.3%). Studies have shown that T-ALL is more commonly associated with low socioeconomic status. This finding may be related to increased frequency of viral infections [11,21,22]. The male preponderance in our patients was probably another important contributory factor for increased occurrence of T ALL in our patients. Akin to our observations, other studies have also demonstrated the differences in clinical and laboratory parameters between T and B-lineage ALL patients [3,4]. Even though males were more frequent in the T-ALL group as compared to B lineage ALL group, the difference was not statistically significant due to high degree of male preponderance (male: female-3.4: 1) in the study population.

Contemporary studies from major centers in the world have stratified T-ALL into a different risk group for treatment and most investigators report an overall inferior outcome in it compared to B-lineage ALL [13-17]. In a study by Children Cancer Group

WHAT IS ALREADY KNOWN?

- T-lineage ALL is associated with high-risk features and adverse prognosis

WHAT THIS STUDY ADDS?

- Using traditional risk group criteria to prognosticate pediatric leukemia patients may not be appropriate, especially in Indian children. T-cell ALL has survival outcome equivalent to B-lineage ALL in the present study.

(CCG) where patients were stratified into risk groups based on age, WBC criteria irrespective of the immunophenotype, T-lineage patients treated with CCG-1800 protocol had a slightly better outcome than B-lineage patients (5 year EFS of 75.2 *vs* 70.9, respectively) [20]. The EFS of T lineage patients (49.9±7.4) was much similar to that of B lineage patients (47.5±5.1) in our study group, even though inferior to that of T-lineage patients from Western studies. In another study from TMH, Mumbai, in which all patients were uniformly treated with the MCP 841 protocol, immunophenotype was not a significant predictor of EFS [19]. The inferior survival outcome as compared to western series is probably due to high risk features at presentation and social, demographic, financial, infrastructual and epidemiological constraints [21-23].

In our study the NCI high risk patients in the T-ALL had a significantly better EFS than the high risk patients in the B lineage ALL. These findings were in consonance with the observations by CCG group, where a subset of patients with high risk leukemia and T-lineage immunophenotype was associated with a significantly more favorable outcome than B lineage immunophenotype, but with T subtype getting more intensive therapy.

Since all our patients were treated uniformly with a single treatment regimen, it would be tempting to conclude that T immunophenotype did not have an adverse impact on prognosis. However, the markedly inferior outcome in the high risk B lineage ALL and standard-risk T-ALL group contributed to the similar outcomes seen in the T and B lineage ALL**.** Our data showed that none of the traditionally described clinical and laboratory prognostic factors were predictive of outcome in T-ALL, akin to the observations of Pullen, *et al*. [24]. In contrast, other investigators have reported gender and WBC count as significant predictors of outcome in T-ALL [13, 25]. In our study, the lack of significance of any risk factor may be explained by the small sample size; a high toxicity-related death rate, especially in the B-lineage ALL group; and the presence of extensive disease at presentation in the majority of our patients. These could also plausibly indicate the limitations and consequences of use of a single therapy regimen in all risk groups instead of contemporary risk-adapted therapy.

Different studies have used different criteria for maturational stage stratification. The criteria used to define maturational stages of T cell ALL in our study were similar to that by Uckun, *et al*. [26]. Majority of their patients belong to immature T-ALL group (248/407, 60.9%) unlike our study, where mature T-ALL was the commonest (53.3%). The mature T-ALL patients had the best outcome (6 year EFS 77.7%) unlike our patients where immature T-ALL had the better outcome (61.4±10.8). Small numbers plausibly preclude identification of specific prognostic factors in these subgroups.

In conclusion, T-ALL occurred more frequently in our population and was clearly associated with high-risk features at presentation. The dismal prognosis of high risk B-lineage and standard risk T-lineage ALL patients indicates the need to select this group for treatment modification and indicate the need of reappraisal of out protocols.

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