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Clinical Profile and Induction Outcome of Children with T-cell Acute Lymphoblastic Leukemia and T-cell Lymphoblastic Lymphoma

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ABSTRACT

Objective: To study the clinical profile and induction outcome in children diagnosed with T-cell acute lymphoblastic leukaemia and lymphoblastic lymphoma.

Study Design: Cross-sectional study.

Place and Duration of Study: Paediatric Oncology Unit, Combined Military Hospital, Rawalpindi Pakistan, from Jan 2012 to Dec 2020.

Methodology: One hundered and twenty-one diagnosed patients of T-ALL and LBL were evaluated with bone marrow biopsy and Contrast-enhanced CT scan of the active region after induction chemotherapy with Dexamethasone, Vincristine, Asparaginase and Daunorubicin along with intrathecal Methotrexate. This was carried out on days-8 and 29 to determine the early remission status and end of induction response, respectively.

Results: Out of 121 patients, 99(81.8 %) had T–ALL, while 22(18.18%) had LBL. Day-8 assessment showed that 94(77.7%) patients were rapid early responders, 24(19.4%) were slow early responders, while 3(2.4%) patients expired before the day eight assessment. Day-29 bone marrow assessment of 88 T-ALL patients showed complete remission in 77 patients (87.5%), incomplete remission in 5(5.68%) patients and treatment failure in 2(2.27%) patients. 20(93.1%) patients with LBL achieved remission by Day-29, while 2 (0.02%) LBL patients died before the Day-29 assessment.

Conclusion: The remission induction rates and mortality rates in our setup are encouraging and comparable to international data. Further improvements can be made by early management of the affected cases and more accessible pediatric oncology health services.

Keywords: Induction outcome, T-cell acute lymphoblastic leukaemia, T-cell lymphoblastic lymphoma.

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy, comprising up to 25% of all childhood cancers, with T-cell acute lymphoblastic leukaemia (T–ALL) accounting for 10%–15% of the cases of pediatric ALL.[1] ALL results from the malignant transformation of B- and T-lineage lymphoid precursors and is caused by several genetic abnormalities such as chromosome translocations, mutations or aneuploidies in genes responsible for cell cycle regulation and lymphoid cell development.[2]

T-ALL is distinguished by malignant lymphoblasts' massive invasion of bone marrow, showing immature T-cell surface markers.[3] Pediatric patients with T-ALL are usually associated with adverse clinical features, such as age of more than ten years, elevated TLC or central nervous system involvement.[4] In addition, due to immature thymocytes' elevated cell division rates, T-ALL is linked with increased cell turnover and tumour burden, along with enhanced chances of a large thymic mass or pleural effusion.[5] Over the years, response rates prognosis for T-ALL was lower compared to B-cell lymphoblastic leukaemia (B-ALL). However, with improvements in treatment, survival rates have become markedly better and now exceed 85%.[6] Still, the outcome for Tcell ALL is unfavourable compared to Bcell ALL in most of the research studies performed.[7]

T-cell lymphoblastic lymphoma (T-LBL) accounts for approximately 20% of pediatric patients' non-Hodgkin lymphomas (NHLs). It is represented by immature T cells' extensive invasion of the mediastinum and other lymphoid organs.[8] T-LBL and T-ALL are postulated to depict distinct presentations of the same illness with malignant T cells of LBL identical to T-ALL and a cutoff of 25% in bone marrow established diagnosis of leukaemia. In contrast, less marrow involvement indicated a lymphoma diagnosis.[9] Most patients suffering from T-ALL are subjected to a blend of

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various chemotherapeutic agents carried out sequentially during the induction, intensification and maintenance phases.[10] T-LBL and T-ALL are classified as NCI high-risk and treated with four drugs in induction, including vincristine, asparaginase, gluco-corticoids and anthracyclines. Studies uniformly demonstrated improvement in an overall remission duration.[9] The proportional correlation of elevated white blood cell count and poor prognosis found in B-ALL is not strictly a feature of T-ALL. Therefore, allogenic bone marrow transplantation is left as the singular curative treatment for relapsed/refractory (R/R) patients.[10]

This study aimed to study the clinical profile and induction outcome in pediatric patients diagnosed with T-cell acute lymphoblastic leukaemia and lymphoblastic lymphoma. Although substantial international and scanty national data on clinical characteristics and treatment outcomes of ALL patients is available, such data pertaining specifically to the T-cell subtype is considerably deficient, primarily due to insufficient pediatric oncology setups in Pakistan. Our study will be the first such study that deals with pediatric T-ALL and LBL patients from a single institute. Therefore, the results from our study will not only be a true representation of the outcome of patients in our setup. However, they can also be compared with similar regional and international studies.

METHODOLOGY

This cross-sectional study was conducted at the Paediatric Oncology Unit, Combined Military Hospital, Rawalpindi, from January 2012 to December 2020. The study was approved by the Institutional Ethical Committee (213/11/21). The sample size was calculated to be 120, taking the incidence of T-cell ALL as 0.13 cases Per 100,00,[11] and the confidence level at 95%.

Inclusion criteria: Both male and female patients, of age one to 16 years, with a diagnosis of T-cell ALL and LBL (based on histopathology, immunophenotyping, cytogenetics and ALL panel) were included in the study through consecutive sampling.

Exclusion criteria: Patients having Philadelphia chromosome, mixed phenotypic ALL and Down syndrome, patients who underwent induction chemotherapy, patients who refused to give consent and non-cooperative patients (psychiatric patients) were excluded from this study to overcome confounding factors and bias in results.

All the patients and their parents/guardians were explained the aim of the study and informed written consent was obtained. Patients' basic demographic and clinical information, such as age, gender, weight, pallor, temperature, bruising, active bleeding, bone pains, cough, respiratory symptoms and cervical lymphadenopathy, were noted. In addition, other important parameters like reporting time, nutritional status, prior treatment details and socioeconomic status were recorded. Investigation records were also obtained, including complete blood counts and morphology, Bone marrow aspiration/trephine biopsy, immuno-phenotyping, CSF analysis, molecular and cytogenetic findings, and CT scan findings. Lumbar puncture was done to evaluate the CNS status, and patients were classified as CNS 1 (absence of blasts), CNS 2 (<5 WBCs/mm^3 with blasts) and CNS 3(>5 WBCs/mm^3 with blasts) as per standard criteria.

Four drug therapy was started comprising Dexamethasone (6mg/m^2/day x 12 hourly for four consecutive weeks followed by gradual tapering to terminate Steroids by the end of week 5), Vincristine (1.5 mg/m^2/ week for five weeks), Asparaginase (2000 U/m^2/ dose given once daily at day four and day 18 of induction chemotherapy) & Daunorubicin (25 mg/m^2/dose weekly as an infusion for consecutive four weeks) along intrathecal Methotrexate (dose according to age).

Early remission status was determined at day-8 by bone marrow examination in T-ALL and volumetric assessment by contrastenhanced CT scan in LBL patients. Rapid early response was defined as less than 25% blasts in T-ALL and >35% reduction in tumour mass in LBL patients. The end of induction response was assessed at day 29 by marrow, and CT scans in ALL and LBL patients, respectively.

Complete remis-sion cases were defined as having less than 5% blasts on bone-marrow examination (M1 marrow) while no residual tumour mass on contrastenhanced CT scan in LBL patients. In our study, we defined partial response in cases of T-ALL as having between 5–25% blasts on bone marrow examination (M2 marrow). Induction failure in T-ALL was >25% blasts (M3 marrow) and <35% volume reduction in LBL. Minimal residual disease assessment on marrow was not done due to its non-availability at setup.

Based on the results of the end-of-induction response, T ALL patients who were partial responders were given regimen C consolidation. At the same time, those with induction failure were taken off protocol and given an R3 regimen. All patients with T LBL were continued with regimen C consolidation (Figure).

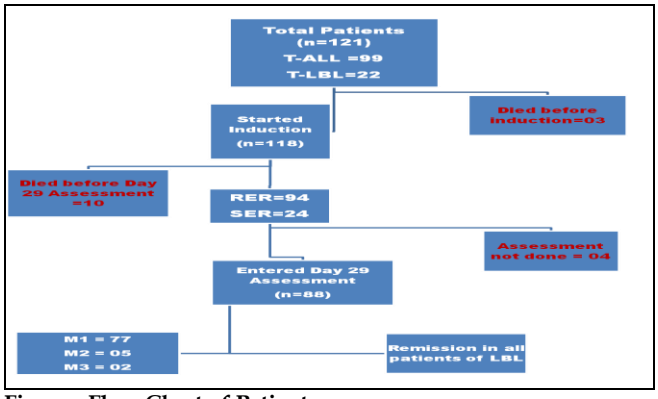

Figure: Flow Chart of Patients

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Categorical data, i.e., qualitative variables, were summarized as frequencies and percentages, while mean and standard deviation were applied to express quantitative variables.

RESULTS

Of 121 patients, 93(76.9%) were males, while 28(23.1%) were females. The mean age was 7.30±3.76 years, with 13(10.7%) patients less than three years of age, 74(61.2%) patients between 3 to 10 years of age and 34 (28.1%) patients more than ten years of age. Fever was seen in 89(73.6%) patients, pallor in 98 (81.0%) and lymphadenopathy was seen in 102 (83.67%) patients. Seventy-three patients had high TLC >50,000 (60.3%) and 93 patients had thrombocytopenia (75.2%). Out of 98 clinically pale children, 78(79.5%) had haemoglobin of less than 10 gm/dl.

Four patients had taken prior treatment, one in the form of steroids, while three had taken chemotherapy. Cytogenetics and ALL panel molecular studies revealed four patients with good prognostic factors. Two had hypertetradiploidy, two with hyperdiploidy, one with high-risk cytogenetic MLL-MLL10, and none had BCR-ABL. CNS-3 was present in only 3(2.27%) patients, while only 1 had CNS-2.

Ninety-nine (81.8%) had T–ALL, while 22 had LBL. Day-8 assessment showed RER in 94(77.7%) patients, while 24(19.8%) patients had SER. Three patients expired before the Day-8 assessment, while ten further expired before the Day-29 assessment. Out of these 13 patients who expired, 4(30.1%) patients expired due to neutropenic sepsis, 6(46.1%) due to respiratory failure, and 3(23.1%) patients died of bleeding. Day- 29 bone marrow assessment of 88 T-ALL patients showed M1 marrow in 77 patients (87.5%), M2 in 5 (5.68%) and M3 in 2(2.27%%) patients who were considered induction failure. Day- 29 bone marrow assessment of four patients was not done due to COVID-19 and critical condition. Out of 20 patients with LBL, all assessed patients achieved remission.

Due to high-risk features and intensive chemotherapy, a significant number of patients developed infections, 86(71.1%) with 13(10.7%) proven or probable fungal infections. Other significant side effects were myopathy in 76(62.8%), while hepatotoxicity was seen in 3(2.5%) patients, neuropathy in 7(5.8%), mucositis in 5(4.1%), hyperglycemia in 4(3.3%) and hypertension was seen in 3(2.1%) cases. Three patients with induction failure were shifted to the R3 protocol. In comparison, 37 patients received Regimen C consolidation with 20 T-LBL and 15 with SER and one with high-risk cytogenetics and another due to Early T-cell precursor lymphoblastic leukaemia, considering the high incidence of relapse. Eight patients died before receiving consolidation. The remission rate on day-29 was 76.03%. None of the inducted patients abandoned treatment (Table).

DISCUSSION

Acute lymphoblastic leukaemia (ALL) is an aggressive tumour characterized by abnormal expansion and differentiation of a clonal population of lymphoid cells.[4] Earlier associated with a dismal prognosis, marked improvements in survival rates have been observed in children with T-ALL owing to newer treatment modalities.[12,13] In our study, 76.9% were male while 23.1% were female, with male to female ratio of 3.3:1. A study conducted by Liao *et al.* on the outcome of T-cell acute leukaemia/lymphoma patients also showed a similar male-to-female ratio of 2.5:1.[14]

Our study showed the mean age of patients as 7.3±3.76, with 10.7% patients less than three years of age, 61.2% between 3 to 10 years of age and 28.1% more than ten years of age. This is similar to the study by Bajel *et al*. carried out on the children with ALL in India, which depicted a mean age of 6 years with most patients less than nine years of age.[15]

In our study, a day eight assessment was done, which showed RER in 77.7% of patients while 19.8% of patients had SER. Wei *et al.* conducted a study on the outcome of early treatment responses in childhood T-cell acute lymphoblastic leukaemia.[16] In this study, a Day-15 assessment was carried out, which revealed RER in 84.6% of patients and SER in 15.6%. The results of this study are in agreement with our study.

Table: Demographic and Clinical Information of the Patients (n=121)

Characteristics	Frequency (%)
Total Number of Patients	121 (100%)
Gender	
Male	93 (76.9)
Female	28 (23.1)
Age in Years	
(Mean±SD)	7.30±3.76
<3 years	13 (10.7)
4-10 years	74 (61.2)
>10 years	34 (28.1)
Weight in Kg	
(Mean±SD)	23.00 ±12.49
<20 Kg	66 (54.6)
21 – 40 Kg	42 (34.7)
>41 Kg	13 (10.7)
Nutritional Status	
Well-nourished	94 (77.7)
Moderately malnourished	15 (12.4)
Severely malnourished	12 (9.9)
WBC count (× 109/L)	
(Mean+SD)	162.60±8.10
<50,000	48 (39.6%)
50,000 – 100,000	11 (9.1%)
More than 100,000	62 (51.3%)
Haemoglobin	
(Mean+SD)	8.90±6.60
<7g/dl	33 (27.4)
>7-10g/dl	44 (36.3)
>10g/dl	44 (36.3)
Platelets count (× 109/L)	
(Mean+SD)	131.0±166.26
<50	56 (46.2)
>50-100	30 (24.8)
>100	35 (28.9)
CNS Disease (n=121)	
CNS1	117 (96.7)
CNS2	01 (0.8)
CNS3	03 (2.5)
Clinical presentation (n=121)	
Fever	89 (73.6)
Pallor	98 (80.9)
Lymphadenopathy	102 (83.7)
Bruising	38 (31.4)
Immunophenotype (n=121)	
Pre B + T-ALL	01 (0.8)
Pre T- ALL	01 (0.8)
T-ALL	97 (80.2)
T-LBL	22 (18.2)
Molecular/cytogenetics (n=121)	
Hypertetraploidy	02 (1.6)
Hyperdiploidy	02 (1.6)
MLL-MLL10	01 (0.8)
Prior treatment (n=4)	
Steroids	01 (25)
Chemotherapy	03 (75)
Complications (n=121)	
Infections	86 (71.1)
Myopathy	76 (62.8)
Neuropathy	07 (5.8)
Hepatotoxicity	03 (2.5)
Mucositis	05 (4.1)
Hypertension	03 (2.5)
Hyperglycemia	04 (3.3)
Invasive Fungal infections	13 (10.7)

A total of 13(10.7%) patients expired, in our study, during the induction phase. Out of these 13, 4(30.1%) patients expired due to neutropenic sepsis, 6(46.1%) due to respiratory failure, and 3(23.1%) died due to bleeding. In addition, Fadoo et al. conducted a study on the clinical features and induction outcome of childhood acute lymphoblastic leukaemia, revealing that 8.6% of children died during induction with infection as the major cause of mortality.[17]

In our study, 83.5% of patients achieved complete remission. Burns *et al.* showed that 88% of the patients in his study achieved complete remission.[18] The results of our study are coincident with other regional and international studies carried out on this topic. However, there may be minor differences in results due to differences in sample size and population subset. Another difference is that our study dealt exclusively with T-cell ALL and LBL, both high-risk. Most studies deal with either pre-B and B-cell ALL or encompass all types of ALL. Studies solely on T-cell ALL and LBL are extremely scarce in the pediatric population.

Recent advancements in diagnostics, including complex cytogenetic and detailed immunophenotypic analysis, to comprehensively rule out early T-cell precursor leukaemia. Similarly, newer therapeutic agents include Nelarabine and the use of chimeric antigen receptor (CAR) T cells.[19] However, these are newer and more expensive treatment options with limited availability, which can improve the outcome in relapsed and resistant cases.

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LIMITATIONS OF STUDY

The minimal residual disease (MRD) at day-29 was not assessed, due to the non-availability of this diagnostic modality at our setup.

CONCLUSION

The remission induction rates and mortality rates in our setup are encouraging and comparable to international data. However, further improvement can be made by early management of the affected cases and more accessible pediatric oncology health services.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AA: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

FN & SS: Drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

MT: Drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

TF & TG: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Bhojwani D, Yang JJ, Pui CH. 2015. Biology of childhood acute lymphoblastic leukemia. Pediatr Clin North Am 2015; 62(1): 47-60. doi: 10.1016/j.pcl.2014.09.004.
2. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med 2015; 373(16): 1541-152. doi: 10.1056/NEJMra1400972.
3. Belver L, Ferrando A. The genetics and mechanisms of T cell acute lymphoblastic leukaemia. Nat Rev Cancer 2016; 16(8): 494-507. doi: 10.1038/nrc.2016.63.
4. Winter SS, Dunsmore KP, Devidas M, Wood B, Esiashvili N, Chen Z et al. Improved Survival for Children and Young Adults With T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization. J Clin Oncol 2018; 36(29): 2926-2934. doi: 10.1200/JCO.2018.77.7250.
5. Sanchez-Martin M, Ferrando A. The NOTCH1-MYC highway toward T-cell acute lymphoblastic leukemia. Blood 2017; 129(9): 1124-1133. doi: 10.1182/blood-2016-09-692582.
6. Möricke A, Zimmermann M, Valsecchi M, Stanulla M, Biondi A, Mann G, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. Blood 2016; 127(17): 2101-2112. doi: 10.1182/blood-2015-09-670729.
7. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol 2019; 20(3): e142-e154. doi: 10.1016/S1470-2045(19)30031-30032.
8. Kroeze E, Loeffen JLC, Poort VM, Meijerink JPP. T-cell lymphoblastic lymphoma and leukemia: different diseases from a common premalignant progenitor? Blood Adv 2020; 4(14): 3466-3473. doi: 10.1182/bloodadvances.2020001822.
9. Murtaza H, Ghafoor T, Iqbal M. Remission Rate Of Pre-B All (Acute Lymphoblastic Leukemia) After Induction Chemotherapy Following United Kingdom Acute Lymphoblastic Leukaemia 2011 (UKALL 2011) Trial Protocol. Pak Armed Forces Med J 2011; 71(2): 469-472. doi: 10.51253/pafmj.v71i2.2966.
10. Seibel NL. Treatment of acute lymphoblastic leukemia in children and adolescents: Peaks and pitfalls. Hematology Am Soc Hematol Educ Program 2008; 374-380. doi: 10.1182/asheducation 2008. 1(1): 374.
11. Raetz EA, Teachey DT. T-cell acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2016 ;2016(1):580-588. doi: 10.1182/asheducation-2016; 1(1): 580.
12. Follini E, Marchesini M, Roti G. Strategies to Overcome Resistance Mechanisms in T-Cell Acute Lymphoblastic Leukemia. Int J Mol Sci 2019; 20(12): 3021. doi: 10.3390/ijms20123021.
13. Guru Murthy GS, Pondaiah SK, Abedin S, Atallah E. Incidence and survival of T-cell acute lymphoblastic leukemia in the United States. Leuk Lymphoma 2019; 60(5): 1171-1178. doi: 10.1080/10428194.2018.1522442.
14. Liao HY, Sun ZY, Wang YX, Jin YM, Zhu HL, Jiang NG. [Outcome of 126 adolescent and adult T-cell acute leukemia/lymphoma patients and the prognostic significance of early T-cell precursor leukemia subtype]. Zhonghua Xue Ye Xue Za Zhi 2019; 40(7): 561-567. Chinese.
15. Bajel A, George B, Mathews V, Viswabandya A, Kavitha M, Srivastava A, et al. Treatment of children with acute lymphoblastic leukemia in India using a BFM protocol. Pediatr Blood Cancer 2008; 51(5): 621-625. doi: 10.1002/pbc.21671.
16. Wei W, Chen X, Zou Y, Chang L, An W, Wan Y, et al. Prediction of outcomes by early treatment responses in childhood T-cell acute lymphoblastic leukemia: a retrospective study in China. BMC Pediatr 2015; 15: 80. doi: 10.1186/s12887-015-0390-z.
17. Fadoo Z, Nisar I, Yousuf F, Lakhani L, Ashraf S, Imam U et al. Clinical features and induction outcome of childhood acute lymphoblastic leukemia in a lower/middle income population: A multi-institutional report from Pakistan. Pediatr Blood Cancer 2015; 62(10): 1700-1708. doi: 10.1002/pbc.25583.
18. Burns MA, Place AE, Stevenson KE, Gutiérrez A, Forrest S, Pikman Y et al. Identification of prognostic factors in childhood T-cell acute lymphoblastic leukemia: Results from DFCI ALL Consortium Protocols 05-001 and 11-001. Pediatr Blood Cancer 2021; 68(1): e28719. doi: 10.1002/pbc.28719.
19. Inaba H, Pui C. Immunotherapy in pediatric acute lymphoblastic leukemia. Cancer Metastasis Rev 2019; 38(4): 595-610. doi: 10.1007/s10555-019-09834-0.