Clinical Features and Treatment Outcome of Pediatric Lymphoblastic Lymphoma at South Egypt Cancer Institute

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Abstract:

Background: Lymphoblastic lymphoma (LBL) and acute lymphoblastic leukemia (ALL) are distinct malignancies arising from immature B or T-cell precursors, classified by the World Health Organization. Differentiating them relies on blast cell percentages in bone marrow, often 20-25%. LBL treatment strategies have shifted from high-grade NHL protocols to ALL-based approaches. The study aimed to present the clinical characteristics, overall survival (OS), event-free survival (EFS), and common chemotherapy-related toxicities observed in patients diagnosed with lymphoblastic lymphoma (LBL) over an 8-year period, spanning from January 1st, 2014, to December 31st, 2020.

Methods: A retrospective cohort analysis was conducted on a cohort of 29 patients diagnosed with LBL and treated using a modified St. Jude TXIII-B high-risk protocol.

Results: The cohort had a mean age of 6.21 ± 3.08 years, with 16 patients (55.2%) being males and 13 patients (44.8%) females. Primary symptoms included difficulty in breathing (51.7%), weight loss (44.8%), peripheral lymph node enlargement (31.0%), fever (31.0%), and pallor (17.2%). All patients presented with advanced-stage disease, with 82.8% at stage III and 17.2% at stage IV. Imaging studies revealed nodal involvement in 31% and extra-nodal involvement in 69% of patients. Hemoglobin levels were ≥ 8 g/dL in 82.8%, kidney function was normal in 72.4%, and 58.6% had LDH levels ≥ 500 U/L. Albumin levels were ≥ 30 mg/dL in 96.6%. Immunophenotyping confirmed T-cell origin (CD3 positive, CD20 negative) in all patients. Bone marrow involvement was observed in 17.2%, and cerebrospinal fluid involvement in 3.4%. Complete remission was achieved in 75.9% of patients, while relapse occurred in 17.2%. Seven patients (24.1%) died, with relapse and severe infection being major contributors. Treatment-related toxicities included myelosuppression (86%), mucositis (62%), and hepatotoxicity (62%). The 4-year OS and EFS were 85 ± 7.5%and 78.6 ±3.4% respectively.

Conclusion: The study's findings align with similar research on LBL treatment. Patients with relapse had poor outcomes, emphasizing the need to identify prognostic factors like minimal residual tumors for better chemotherapy response evaluation. The study also noted specific chemotherapy-related side effects, calling for careful treatment planning and management strategies.

Keywords: Lymphoblastic lymphoma, clinical features, treatment outcomes, treatment morbidities.

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Introduction:

Non-Hodgkin's lymphomas are cancers originating from lymphoid cells in the immune system. The World Health Organization classification divides NHL into B-cell and T-cell/natural killer cell lymphomas. T-cell lymphomas include precursor neoplasms like lymphoblastic lymphoma (LBL) and more mature peripheral T-cell lymphomas [1, 2].

Most LBLs originate from T-cell precursors and express T-cell markers like CD1a, CD2, CD3. They efface lymph node architecture and consist of small lymphoblasts with little cytoplasm [3].

T-LBL is characterized by the malignant proliferation of lymphoid cells in various immune system sites, including lymph nodes, bone marrow, spleen, liver, and gastrointestinal tract [1]. Unlike the

low-grade and clinically indolent NHL subtypes that predominate in adults, T-LBL in pediatric cases is predominantly high-grade and exhibits aggressive clinical behavior [4].

Clinical presentation of T-LBL often includes an anterior mediastinal mass, leading to symptoms such as dyspnea, wheezing, stridor, dysphagia, or swelling in the head and neck. Involvement of other sites like lymph nodes, bone, skin, central nervous system (CNS), and abdominal organs may also occur [2].

Treatment for T-LBL involves intensive multi-drug chemotherapy protocols, typically used in leukemia, along with intrathecal chemotherapy. These protocols have shown high disease-free survival rates, exceeding 90% for low-stage T-LBL and surpassing 80% for high-stage T-LBL [5, 6].

Mediastinal radiation is usually unnecessary except in emergency situations where there is superior vena cava or airway obstruction. The implementation of an ALL approach, consisting of induction, consolidation, and maintenance therapy over 24 months, has significantly improved survival rates in T-LBL [7].

However, recurrent or refractory T-LBL poses significant challenges, with survival rates ranging from 10% to 40% [8]. Currently, there are no standard treatment options for such cases. Some potential treatment options include nelarabine-containing chemotherapy regimens, the ICE regimen (ifosfamide, carboplatin, and etoposide), bortezomib-based regimens, and allogeneic stem cell transplantation [9-12]

The aim of this work is to report the clinical characteristics, overall survival (OS), event free survival (EFS), and common chemotherapy toxicities of LBL patients treated at the Pediatric Oncology Department of the South Egypt Cancer Institute (SECI), Assiut University, spanning from January 1st, 2014, to December 31st, 2021.

Patients and Methods:

Study Population

This retrospective cohort analytic study was conducted at the Pediatric Oncology Department of the South Egypt Cancer Institute (SECI), Assiut University, spanning from January 1st, 2014, to December 31st, 2020 then follow up for one year at least. The study exclusively pertains to pediatric patients diagnosed with T-cell Lymphoma, specifically Lymphoblastic Lymphoma (LBL). Ethical considerations were rigorously adhered to, with approval obtained from the Institutional Ethical Committee, and informed consent was secured from the families of all participating children.

The inclusion criteria encompassed boys and girls under the age of 18 years, bearing histopathological documentation of NHL (T-Lymphoblastic Lymphoma). Importantly, patients were limited to those newly diagnosed with NHL, excluding any individuals with prior chemotherapy and/or radiotherapy history, HIV related NHL, post-transplant associated NHL patients, NHL associated 1ry immunodeficiency, and NHL as a secondary malignancy were also excluded from the study.

Data Collection

Patient data was meticulously gathered from medical records, encompassing the following:

Demographic Data: such as age, gender, and the date of initial diagnosis were recorded.

Clinical Presentation: data collected from files as the presence and duration of symptoms, like pallor, bleeding tendencies, bone pain, cough, dyspnea, abdominal pain or distension, and swellings.

Physical Examination: data collected from files involved the patient's general condition and the presence of lymphadenopathy in nodal areas (abdominal, mediastinal, and peripheral), extra-nodal manifestations (such as tonsillar enlargement and organomegaly), and signs of bone marrow (BM) involvement, such as bone pain, pallor, and bleeding. CNS (Central Nervous System) affection, which includes convulsions, increased Intra-Cranial Tension (ICT), and motor and sensory deficits.

Laboratory Studies: Reporting any performed laboratory investigations as complete blood counts (CBC) with total and differential counts, kidney function tests measuring blood urea and serum creatinine levels, liver function tests, evaluation of Lactic Dehydrogenase (LDH) levels, Uric Acid levels, and Tumor Lysis Profile. Additionally, bone marrow (BM) aspirate and biopsy along with cerebrospinal fluid (CSF) cytology were performed

Radiological Studies: Reporting any performed radiological studies as Chest X-ray (CXR), conducted in postero-anterior and lateral views to detect mediastinal masses, pleural effusion, or pericardial effusion. Local Ultrasonography (U/S) on cervical, axillary, and abdominal regions at the time of diagnosis and throughout treatment, including post-treatment follow-ups. Multi-Slice Computed Tomography (MSCT) Scans to the primary tumor site, covering areas mainly the neck and chest. They were initially employed for staging and to monitor responses to chemotherapy, with follow-up scans conducted after completing treatment. Echocardiograms were done to assess cardiac function and establish a baseline for further follow-ups. Bone scans were implemented when patients presented with bone masses

Pathological Studies: True cut needle biopsy samples were obtained from the inaccessible masses or excisional LN Biopsy from presenting lymph nodes. These specimens underwent thorough histopathological studies, including immunohistochemical tests.

Staging and Risk Stratification

Patients diagnosed with LBL were staged into early stage (I and II) or late stage (III and IV) using the Murphy staging system (Murphy et al., 1980) [13].

Treatment Protocols

Patients with LBL received treatment according to a modified St. Jude TXIII-B high-risk protocol (Pui et al., 2004) [14].

Treatment Outcome

Patients were rigorously monitored throughout and after treatment. Response evaluations were conducted clinically, through laboratory assessments, and via imaging studies. Following treatment completion, patients were followed for a minimum of 1 year to assess overall survival (OS) and event-free survival (EFS) at specified intervals.

Treatment related Morbidity

Chemotherapy toxicity was assessed according to WHO Common Terminology Criteria for Adverse Events (CTCAE) (CTCAE Version 5.0, 2017).

Statistical analysis

All statistical calculations ware done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Quantitative data were statistically described in terms of mean ± SD and median and range when not normally distributed. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using Kruskal Wallis test or Mann Whitney U test because the data were not normally distributed. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Overall Survival (OS) was calculated for all patients as the time interval from the date of diagnosis of the disease to the date of last follow up or date of death for any cause, Event free survival (EFS) was calculated for all studied cases from the date of admission up to the date of the event (relapse, death, disease progression, or loss of follow up). Both were estimated with Kaplan-Meier method and differences were assessed by the log-rank test. Cox regression was calculated to determine significant factors associated with mortality. P-value is always 2 tailed set significant at 0.05 levels.

Results:

This study included 29 patients who were diagnosed and treated as LBL during the period from January 1st, 2014, to December 31st, 2020. The Mean age of the studied patients was 6.21 ± 3.08 years ranged from 2 years to 15 years. 16 patients (55.2%) were males and 13 patients (44.8%) were females.

The main presenting symptoms were difficulty in breathing in 15 patients (51.7%), followed by weight loss in 13 patients (44,8%), peripheral lymph node enlargement in 9 patients (31.0%), fever in 9 patients (31.0%) and 5 patients had pallor (17.2%).

All LBL patients were advanced stage, 24 patients (82.8%) were stage III and 5 patients (17.2%) were stage IV LBL.

Imaging studies diagnosed nodal site in 9 patients (31%) while Extra nodal affection was reported in 20 patients (69 %). Nodal involvement was Lymphadenopathy in 3 patients (10.3%), and mediastinal lymphadenopathy in 6 patients (20.7%).

Table 1 Demographic and Clinical Characteristics of studied Patients.

Variable	**LBL (n=29)**	
Age (years)		
• Mean ± SD	6.21 ± 3.08	
• Median (range)	5 (2 – 15)	
Sex		
• Male	16	(55.2%)
• Female	13	(44.8%)
• Male : Female ratio	1.2:1	
General presentation		
• Fever	9	(31.0%)
• Pallor	5	(17.2%)
• Weight loss	13	(44.8%)
* Difficulty in breathing	15	(51.7%)
* Peripheral lymph node enlargement	9	(31%)
Anatomical site		
- Nodal	**9**	(31.0)
- Extra-nodal and nodal	**20**	(69.0)
Staging		
• III	24	(82.8)
• IV	5	(17.2)

Extra nodal involvement were mediastinal with pleural effusion in 10 patients (34.5 %), 5 patients (17.2%) had HSM, 4 patients (13.8%) had BM infiltration and 1 patient (3.4%) had BM and CNS infiltration.). Table 1 describes Demographic and Clinical Characteristics of Patients.

The majority of patients (82.8%) had hemoglobin levels equal to or greater than 8 g/dL, indicating the absence of profound anemia. Kidney function tests revealed that approximately 72.4% of patients had normal results, while 27.6% displayed abnormal kidney function.

Table 2 Laboratory Characteristics of the studied Patients

Variable	All Patients (n=29)
Hemoglobin	
• ≥ 8	24 (82.8%)
• < 8	5 (17.2%)
Kidney function test	
• Normal	21 (72.4%)
• Abnormal	8 (27.6%)
LDH	
• < 500	12 (41.4%)
• ≥ 500	17 (58.6%)
Albumin level	
• ≥ 30 mg/dl	28 (96.6%)
• < 30 mg/dl	0 (0.0%)
BM involvement	5(17.2%)
CSF involvement	1 (3.4%)

The analysis of lactate dehydrogenase (LDH) levels showed that 58.6% of patients had LDH levels equal to or exceeding 500 U/L. Notably, 96.6% of patients had albumin levels greater than or equal to 30 mg/dL. All patients were confirmed by IHC as CD20 -ve & CD3+ve confirm diagnosis of LBL. Additionally, 17.2% of patients had bone marrow involvement, and 3.4% exhibited cerebrospinal fluid involvement as shown in Table 2.

Twenty patients (69%) achieved CCR, Twenty two (75.9%) achieved CR five patient (17.2%) developed relapse (relapse occurred at primary site), and 7 patients (24.1%) died (three patients after relapse, 4 patients from severe infection and septic shock) as in table 3.

Table 3 Treatment outcome of studied patients

Variable	All patients=29
CCR	20(69%)
CR	22 (75.9%)
Relapse	5 (17.2%)
Deaths in relapse	3 (10.3%)
Deaths in remission	4 (13.8%)

Regarding morbidities (Table 4) Myelo-suppression in (86%) followed by Mucositis in (62%), Hepatotoxicity (62%).

Table 4 Treatment Related morbidities of studied patients

Variable (N=29)	All Patients
BM suppression (grade II-III)	25 (86%)
GIT	
1-Mucositis (grade III- IV)	18 (62%)
2-Typhilitis	5 (17 %)
3-Hepatotoxicity • Grade II-III	18 (62%)
Infectious complications	
1-Chest infections:	9 (31%)
• Bacterial pneumonia	7 (78%)
• Fungal pneumonia	2 (22%)
2-Sepsis	4 (14%)
3- HCV	2 (7%)
4- Gastroenteritis	9 (31%)
CNS	
Peripheral neuropathy	1 (3%)
Extravasation	3 (10%)

The median follow-up duration of the 29 LBL patients was 36 months (range 13 to 67 months). The 4 year overall survival (OS) and event free survival (EFS) were 85 ± 7.5%and 78.6 ±3.4%respectively Figures (1,2).

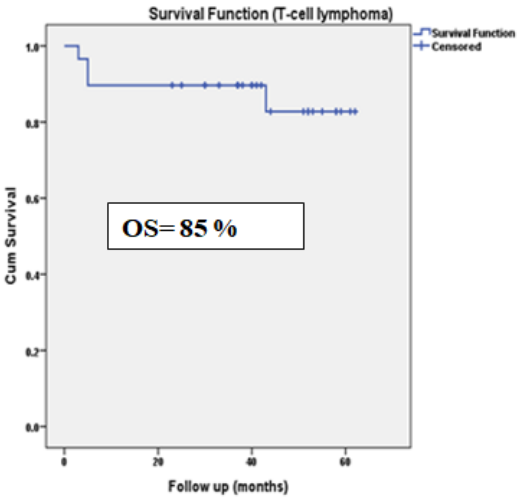

Figure 1: The 4-year OS

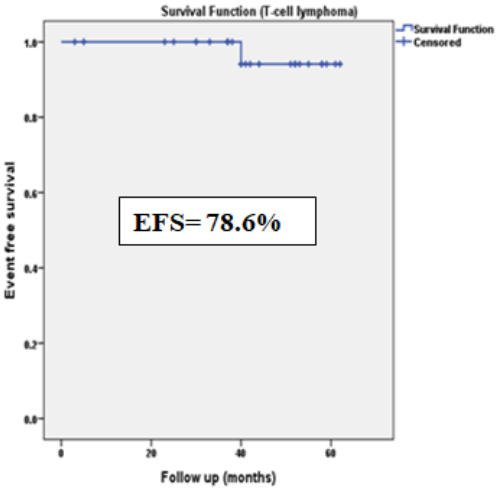

Figure 2: EFS for all studied patients

Discussion:

This report presents the results of a retrospective study including 29 LBL patients treated according to a modified St. Jude TXIII-B high-risk protocol (Pui et al., 2004) [14].

The mean age at diagnosis in this study was 6.21 ± 3.08 years, which is younger than what was reported in other studies ranging from 7 to 8 years [15-21].

The most common primary site of presentation in this study was the mediastinum, with 100% of patients presenting with a mediastinal mass. This finding aligns with previous research that also reported mediastinal mass as the predominant site of presentation, ranging from 72% to 89% of cases [16-18, 20, 22-24].

At diagnosis, the majority (82.8%) presented with stage III disease, while 17.2% had stage IV disease. This is consistent with other studies that reported stage III disease ranging from 50.9% to 62.2% of cases, and stage IV from 16.8% to 42.6% [15-17, 23, 24].

Bone marrow infiltration was found in 17.2% of cases in this study, which is consistent with another study reporting 14.3%, but lower than rates from 21% to 44% in other research [15-17, 23, 24].

Central nervous system infiltration was seen in 3.4% of patients in this study, which is consistent with rates ranging from 0.9% to 3.7% in other studies [15-17, 24, 25].

This study tracked 29 patients over a median follow up of 36 months. Complete remission post-induction chemotherapy was achieved in 75.9% of patients. This contrasts with complete remission rates ranging from 40.3% to 98.7% reported elsewhere [15-17, 24].

Overall survival was 85±7.5% while event-free survival was 78.6 ±3.4%. These rates were lower than what was reported in other studies ranging from 82.2% to 90.2% [16, 24-27].

Relapse/progression occurred in 17.2% of patients, which is consistent with rates ranging from 10.4% to 23.1% reported elsewhere [8, 15-17, 24].

Finally, in addition to optimizing outcomes with risk stratification and improved therapeutic strategies, improving global outcomes for children with NHL will require optimizing diagnostic and treatment approaches for patients in resource-poor settings where most pediatric NHL cases occur and survival remains poor.

Conclusion:

In this study, LBL patients presented with a range of clinical characteristics (but mainly with mediastinal lymphadenopathy) and advanced-stage disease. The majority achieved complete remission following induction chemotherapy. However, a subset of patients experienced relapse or succumbed to various causes, highlighting the need for continued research into prognostic factors and improved treatment strategies for this population. Myelosuppression and other treatment-related toxicities were notable, emphasizing the importance of comprehensive patient care during therapy. The observed overall survival and event-free survival rates indicate promising outcomes, although vigilance in patient management remains essential for optimizing treatment outcomes in LBL.

List of Abbreviations

ALL: Acute lymphoblastic leukemia
BM: Bone Marrow
CNS: Central Nervous System
CXR: Chest X-ray
EFS: Event-free survival
HSM: Hepatosplenomegaly
LBL: Lymphoblastic Lymphoma
LDH: Lactate dehydrogenase
MSCT: Multi-Slice Computed Tomography
NHL: Non-Hodgkin Lymphoma
OS: Overall survival
SD: Standard Deviation
SECI: South Egypt Cancer Institute
TIT: Triple Intrathecal Therapy
TXIII-B: St. Jude TXIII-B high-risk protocol
U/S: Ultrasonography

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Conflict of Interest: The authors declare that they have no conflict of interest

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