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Hematological Malignancies

Initial Experiences in Adolescents and Young Adults with T-Cell Acute Lymphoblastic Leukemia/Lymphoma Treated with the Modified BFM 2002 Protocol in a Resource-Constrained Setting

Prutha Jinwala[1] Rajesh Patidar[1] Shashank Bansal[1] Vikas Asati[1] S.P. Shrivastava[1] Aditya Elhence[1] Swati Patel[2] P.G. Chitalkar[1]

[1] Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences, Indore, Madhya Pradesh, India
[2] Department of Pediatrics, Division of Pediatric Hemato-oncology, Sri Aurobindo Institute of Medical Sciences, Indore-Ujjain highway, Indore, Madhya Pradesh, India

Address for correspondence Prutha Jinwala, MD, Senior Resident, Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences, Indore 453555, Madhya Pradesh, India (e-mail: prutha.jinwala@yahoo.com).

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Abstract

Prutha Jinwala

T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL) in adolescents and young adults (AYAs) is a clinically aggressive malignancy and life-threatening at diagnosis. Intensive chemotherapy protocols, inspired by the Berlin-Frankfurt-Münster (BFM) regimen, along with central nervous system (CNS) prophylaxis, have achieved a 75 to 85% 5-year disease-free survival rate. However, in cases of marrow and CNS relapses, second-line chemotherapy is usually ineffective. This study aimed to assess the safety and efficacy of the BFM 2002 protocol and to correlate clinical profiles and prognostic factors with survival outcomes in AYA T-ALL/LBL patients. We retrospectively analyzed data from T-ALL/LBL patients treated at the Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences (SAIMS), Indore, between 2018 and 2021. Twenty-one patients aged 15 to 29 years were studied for their clinical course and laboratory parameters over 36 months. Diagnosis and risk stratification were performed following the guidelines of the BFM 2002 protocol. All patients received treatment and monitoring according to this pediatric-inspired protocol. The median age of the patients was 17 years (range: 15–28 years). Eleven patients presented with mediastinal lymph node enlargement, 10% exhibited CNS involvement, and none had testicular involvement. Eleven patients had marrow blasts greater than 25%, indicative of acute lymphoblastic leukemia. All 21 patients were treated according to the intensive modified BFM 2002 protocol and achieved morphological remission after a median follow-up of 24 months (range: 18–36 months). Seventeen patients achieved minimal residual disease (MRD) negativity post-induction. MRD at day 33 showed a significant association with the probability of disease relapse ($p = 0.0015$). There were five deaths (24%), one due to toxicity and four due to relapse. The study

Keywords

- Aya
- BFM 2002
- interim response
- MRD
- T-ALL
- T-LBL

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recorded an 18-month overall survival of 76%. These results were achieved despite financial constraints. Data were entered into a spreadsheet, and statistical analysis was performed using IBM SPSS version 23. Continuous data are presented as ranges and medians, while categorical variables are shown as percentages and numbers. A chi-squared test for association, with a significance level set at $p < 0.05$, was conducted as indicated. AYA T-ALL/LBL requires intensive treatment regimens. With biological characterization of LBL/ALL and close therapy monitoring, encouraging outcomes can be achieved even in resource-limited settings.

Introduction

T-cell lymphoblastic lymphoma (T-LBL) and T-cell acute lymphoblastic leukemia (T-ALL) are characterized by neoplastic proliferation of clonal precursor T cells. T-LBL presents with mediastinal involvement with or without other lymphoid organ involvement. Involvement of peripheral blood (PB) and extramedullary organs like the testis and central nervous system (CNS) is possible.[1] Patients with bone marrow blasts less than 25% were diagnosed with T-LBL and T-ALL. While some consider both as distinct entities, most consider them as biological variants of the same malignancy.[2]

Acute leukemia is the commonest pediatric cancer worldwide and in India.[3,4] Pediatric ALL patients achieve a 90% 5-year survival, compared to 40% for older adolescents and young adults (AYAs). The AYAs account for less than a fourth of the ALL burden but contribute to 80% of ALL-related deaths.[5,6] This discrepancy is due to the heterogeneous disease biology, unique host factors, and lack of standard treatment guidelines suitable to young persons. AYAs have been underrepresented in clinical trials, potentially due to the limited number of clinical trials focusing on the AYA subgroup and psychosocial incompatibilities.[7] Over the last decade, AYAs with ALL have been recognized as a distinct population. Aggressive treatment approaches have led to event-free survival (EFS) rates of nearly 70%.[8,9]

We present an institutional experience with a pediatric-inspired modified Berlin-Frankfurt-Münster (BFM) 2002 protocol in AYA T-ALL/LBL patients aged 15 to 29 years.

The goal of this study was to determine the safety and efficacy of this intensive regimen, as well as to correlate the clinical profile and prognostic factors (baseline white blood cell [WBC] count, ploidy, cerebrospinal fluid [CSF] status, minimal residual disease [MRD], toxicities, and infections) on AYA T-ALL/LBL survival outcomes. In doing so, we aimed to standardize the usage of intensive ALL-like regimens to treat T-LBL.

Methods

Patients

A retrospective study of patients with T-ALL/LBL treated at the Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences (SAIMS), Indore, from January 2018 to January 2021 was conducted. All untreated patients (between 15 and 29 years of age) over a period of 36 months, including at least 18 months postdiagnosis, were studied for clinical course and laboratory parameters.

Inclusion Criteria

Patients aged 15 to 29 years of either gender diagnosed with T-ALL/LBL from January 2018 to June 2019, were included in the study.

Exclusion Criteria

- Patients of early precursor T-cell immunophenotype.
- Patients of B-cell phenotype ALL/LBL.

Data were retrieved from the electronic medical records. Additional data including outpatient notes, inpatient records, and discharge summaries were reviewed for clinical characteristics and treatment details using a custom datasheet. Data regarding events (major toxicities, failure to achieve remission; relapse, or death) and the disease status at the 18-month follow-up were recorded.

Diagnosis

Diagnosis of T-ALL/LBL was done using peripheral smear examination, lymph node/bone marrow morphological assessment, and flow cytometry (FCM)/immunohistochemistry. Cytogenetics and ploidy analysis using karyotyping was performed. CNS involvement was determined by CSF cytology and neuroimaging (as indicated). The CNS status was assigned according to the BFM 2002 protocol.[10] Mediastinal involvement on chest X-ray was confirmed by contrast-enhanced computed tomography (CECT) of the thorax/positron emission tomography CT (PET-CT). All the patients underwent testicular ultrasonography to rule out involvement of the testes. Irrespective of bone marrow involvement, all the patients were treated as per the modified BFM 2002 leukemia regimen and followed up. The patients and their family were counseled about the prospects of damage to the patient's fertility and a record thereof was kept. Fertility preservation options were offered.

Risk Stratification

Patients were risk-classified according to the ploidy (hypodiploidy), cytogenetics (HR cytogenetics included $t(4;11)$ and $t(9;22)$ albeit extremely rare in T-cell phenotypes), prednisolone response (day 8 absolute blast count >1,000), and interim MRD positivity (day 33 MRD > 0.01%). Patients

with any of these poor prognostic factors were stratified as high risk (HR), while the rest were classified as intermediate risk (IR). Age at diagnosis being more than 6 years nullified the standard risk category.

Modified BFM 2002 Protocol

All the patients were administered a uniform chemotherapy regimen.[10] The following modifications were made to the original BFM 2002 protocol:

- We adopted the concept of MRD testing from the BFM 2009 protocol into our practice. This allowed treatment escalation at an earlier stage for patients at HR of disease relapse.[11]
- During phase 2 reinduction, 6 mercaptopurine (6MP; 60 mg/m^2) was used instead of 6 thioguanine (6TG).
- Post phase II reinduction, all HR patients or those with T-ALL + WBC >100,000 received either prophylactic cranial radiotherapy (pCRT; 12 Gy) in CNS status 1/2 patients or therapeutic cranial radiotherapy (tCRT; 18 Gy) in all CNS 3 status patients. To compensate for the elimination of pCRT in patients with T-ALL + WBC < 100,000, they received six additional doses of Intrathecal methotrexate every month beginning by the fourth week of the maintenance therapy.[11]

Response Evaluation

At the end of phase I/A induction, assessment of bone marrow morphology and MRD on first-pull aspirate by eight-color FCM were used to assess the response for T-ALL. The M criteria were used to evaluate the patient's bone marrow response; clinical remission was documented if M0 to M1 status (blast cells <5%) was attained.[10] A positive MRD level was defined as one greater than 0.01%. If the MRD test was positive, a second MRD assessment was carried out at later time points (at phase I/B, phase M, or reinduction).[11] In the case of T-LBL, response assessment was done using a PET-CT at the end of induction phase I/A. A Deauville score of ≤3 was considered a complete metabolic response (CMR). In the case of a persistent mass lesion/infiltration, an excisional biopsy was performed. If leukemic blasts were seen in the biopsy specimen, these patients were treated as per the HR category.[12] Relapses were noted. They may be combined or isolated (medullary or extramedullary).[13]

Management of Toxicities

Grade 3/4 toxicities were defined as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 used for reporting and analysis.[14] They were further stratified into disease- and treatment-related complications.

Statistical Analysis

The data were entered into a spreadsheet, and IBM SPSS version 23 was used for statistical analysis. Continuous data are shown as range and median, whereas categorical variables were shown as percentages and numbers. A chi-squared test for association, considering $p < 0.05$ as the level of significance, was calculated as indicated.

Table 1 Clinicopathological characteristics of patients

Patient characteristics		
Number of patients		21
Median age, y (range)		17 (15–28)
Sex	Male	20 (95%)
	Female	1 (5%)
T-LBL		5 (24%)
T-ALL		16 (76%)
Baseline WBC	>100,000	9 (43%)
	<100,000	12 (57%)
Mediastinal mass		11 (52%)
CNS involvement		2 (10%)
Testicular involvement		0%

Abbreviations: CNS, central nervous system; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma; WBC, white blood cell.

Results

Clinical Characteristics

The majority of participants (95%) were males, with a median age of 17 years (range: 15–28; ►Table 1).

At baseline, 16 of 21 patients had marrow blasts >25%, indicating acute lymphoblastic leukemia (ALL). Of these, 9 had an initial WBC count of more than 1,00,000/mm^3. Five were T-LBLs. Eleven had mediastinal lymph node enlargement, while 2 had CNS involvement. None had testicular involvement.

Karyotyping revealed hypodiploidy in three patients (14%).

All 21 patients were treated on the intensive modified BFM 2002 protocol.

Outcomes

Eight were HR (38%) patients and 13 were IR (62%) patients (►Tables 2 and 3). All five LBLs were IR by default. Out of 16 T-ALL cases, a good prednisolone response was seen in 12 (75%) cases.

Table 2 Treatment characteristics

Prednisolone response	PGR	12 (75%)
	PPR	4 (25%)
Interim MRD/CMR	Negative	17 (81%)
	Positive	4 (19%)
Risk	IR	13 (62%)
	HR	8 (38%)
Radiotherapy	Nil	8 (38%)
	pCRT	11 (52%)
	tCRT	2 (10%)

Abbreviations: CMR, complete metabolic response; HR, high risk; IR, intermediate risk; MRD, minimal residual disease; pCRT, prophylactic cranial radiotherapy; PGR, prednisolone good responder; PPR, prednisolone poor responder; tCRT, therapeutic cranial radiotherapy.

Table 3 On follow-up

Treatment status	Completed		9 (43%)	
	Ongoing		6 (29%)	
Disease status	Complete remission		16 (76%)	
	Relapse	Isolated	3 (14%)	
		Combined	2 (10%)	
		Total	5 (24%)	
Median duration of follow-up (mo)			24 (18–36)	
18 mo postdiagnosis	Alive	In CR	15 (71%)	
		With relapse	1 (5%)	
		Total	16 (76%)	
	Dead	In CR	1 (5%)	
		With relapse	4 (19%)	
		Total	5 (24%)	
Relation with interim response	MRD negative/CMR	CR	16 (94%)	$p = 0.0015$
		Relapse	1 (6%)	
	MRD positive/no CMR	CR	0 (0%)	
		Relapse	4 (100%)	
T-LBL	CMR		5 (100%)	$p = 0.819$
	No CMR		0 (0%)	
T-ALL	MRD negative		12 (76%)	
	MRD positive		4 (19%)	

Abbreviations: CR, complete remission; CMR, complete metabolic response; MRD, minimal residual disease; T-ALL T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma.

Morphological remission was observed in all the patients (100%) and MRD was negative in 76% patients with T-ALL postinduction. All five patients with T-LBL (100%) were in CMR on day 33 as documented by PET-CT and they were still in remission (100%) at the last follow-up. Interim MRD/CMR has a significant association with the probability of disease relapse ($p = 0.0015$). Overall, 17 (81%) patients were in CMR/MRD negative postinduction. Five patients had relapsed (24%), of which four (all previously MRD positive) succumbed to the disease. With a median follow-up of 24 months, the overall survival (OS) was 76% at 18 months.

Toxicities

Complications were encountered in all patients during treatment. Disease-related grade 4 complications included pericardial effusion requiring pericardiocentesis in two patients and tumor lysis syndrome requiring dialysis in two patients (►Table 4).

Febrile neutropenia (FN) was the most common treatment-related complication. In all, 19% had grade 3/4 FN. Another common complication was pancreatitis (9.5%). Overall, 33% of patients had grade 3/4 toxicities.

Table 4 Grade 3/4 complications

Disease related	
Pericardial effusion	2 (9.5%)
Tumor lysis syndrome	2 (9.5%)
Treatment related	
Hyperglycemia	1 (4.8%)
Pancreatitis	2 (9.5%)
Febrile neutropenia	4 (19%)
Septic shock	1 (4.8%)
Mucormycosis	1 (4.8%)
Limb gangrene	1 (4.8%)
Aspergillosis	2 (9.5%)
Others	
COVID-19 pneumonia	2 (9.5%)

Discussion

T-ALL comprises 15% of pediatric ALL compared to 25% in AYAs. The incidence of ALL/LBL has increased more in the AYA population in recent decades. These malignancies typically affect older teenagers, and they are more common in men.[1,2] While genetic anomalies that have prognostic implications have been used to stratify B-lymphoblastic cancers, molecular features of T-lymphoblastic malignancies are not prognostic.[2] Mutations like NOTCH1 and PTEN (except LOH 6q) are favorable, but it is yet premature to consider them as actionable or predictive.[1]

The classical presentation of T-lymphoblastic neoplasms with a high proliferative index is a mediastinal mass. The outcome of T-LBL has recently improved with ALL-type chemotherapy with the omission of mediastinal radiotherapy.[15,16] The early precursor fraction responds poorly to the treatment.[17] Treatment failures usually occur within a year of starting treatment, with the mediastinum being the most common site. Functional imaging combining CT with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET-CT) might be more sensitive to detect residual viable tumors and have a prognostic impact.[12,18] Our study mirrors these results with 100% survival of T-LBL patients who had documented CMR in PET-CT at the end of the induction phase of treatment.

McNeer et al reviewed studies comparing outcomes using either adult or pediatric regimens in AYA patients. They have reported better results on pediatric-inspired therapy with increased survival rates, limited hospital admissions, fewer acute and late toxicities, and improved quality of life.[19] The CALGB 10403 study used pediatric protocols for the treatment-naive AYA population. The median EFS was 78.1 months, which was more than double the historical control of 30 months; the 3-year EFS was 59%. The estimated 3-year OS was 73%.[20] This demonstrated the viability and efficacy of pediatric protocols in the AYA population.[20] The Indian study found that AYA ALL treated with the BFM 90 protocol had 59.4% 3-year EFS and 61.8% OS.[23]

Despite a limited sample size and brief follow-up, the results of our study using the modified BFM 2002 protocol are reassuring with an 18-month OS of 76%. A negative interim MRD was associated with improved relapse-free survival. This association has been validated in the BFM 2009 protocol.[11]

Our study reports grade 3/4 toxicities in 33% of patients, with pancreatitis being common (9.5%). Compared to younger patients, asparaginase affects more AYAs with hepatic dysfunction, pancreatitis, and coagulopathies, although the benefits are significant. Compared to children, AYAs had a reduced incidence of peg-asparaginase hypersensitivity. Teenagers are most at risk of steroid-induced avascular osteonecrosis.[24]

A single chemotherapy protocol contributed to the validity of our outcomes. Most patients belong to the low-income and underserved areas of central India. We have tried to mitigate the financial and logistic shortcomings by minimizing the need for hospitalization, using central venous devices, and maintaining them, and administering much of the protocol on an outpatient basis. Despite financial constraints, essential investigations, as indicated, were carried out with the help of nongovernmental organizations (NGOs) (TYAcan, CanKids, Leukemia Crusaders). Using government-aided treatment schemes (PM-JAY), we managed to adhere to the protocol, maintain dose intensity, and attain good CR rates along with minimal treatment-related mortality.

Conclusion

The study has demonstrated the feasibility and efficacy of an intensive protocol in AYA patients with a catastrophic hematological cancer. Despite a short median follow-up of 24 months, the results are encouraging with an OS of 76%. MRD has emerged as a key prognostic indicator of relapse-free survival. Patient-reported outcomes like those in the psychosocial sphere could have added value to the results.

Ethical Approval

This study was conducted per the ethical standards that are consistent with the Helsinki Declaration, the International Conference on Harmonization of Good Clinical Practices, and the applicable legislation on noninterventional studies. The study was approved by the Institutional Ethics Committee (IEC NO: SAIMS/IEC/2021/37). Considering the study's retrospective nature, informed consent was waived.

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None.

Conflict of Interest

None declared.

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