Article published online: 2025-08-26

THIEME OPEN ACCESS

Original Article

Treatment-Related Toxicity Profile in Children with Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma during Induction Chemotherapy: Prospective Insights from a South Indian Cohort

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Ind J Med Paediatr Oncol

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Abstract

Introduction There is limited data on treatment-related toxicity and mortality in children with acute lymphoblastic leukemia (ALL) in resource-limited settings, which is important for anticipation and better prophylactic care.

Objectives This study aims to determine the proportion of children with ALL/T- lymphoblastic lymphoma (T-LL) developing treatment-related toxicity during induction chemotherapy, to study the proportion of mortality, the cumulative duration and frequency of treatment delays, and frequency of treatment protocol modifications.

Materials and Methods It was a prospective cohort study where all consecutive children aged between 1 month and 15 years with ALL/T-LL were included. They were followed up during induction chemotherapy and toxicities were recorded, graded as per the Common Terminology Criteria for Adverse Events grading, and analyzed.

Results One-hundred and one children with median age of 6 years (interquartile range: 3, 11) were enrolled. A total of 696 toxicities were recorded among 101 children, of which 418 (60.06%) were of grades 3 and above, which were studied. Number of grades 3, 4, and 5 toxicities were 236 (33.91%), 176 (25.29%), and 5 (0.72%), respectively; of which 73.2% were hematological and 26.8% were nonhematological. Sixty-five treatment breaks were observed in 51 children (50.49%), with majority (34%) occurring in week 3. Protocol modification was observed in 10 (9.9%) due to toxicities and 9 (8.9%) required intensive care admission. Our induction mortality rate was 8.9%, of which infection-related mortality was observed in 4.9%. A statistically significant association was observed between risk group and toxicities of grade $\geq$ 3, with the nonstandard risk group exhibiting 3.21 times higher odds of experiencing these toxicities compared with the standard risk group.

Conclusion The results obtained from our study showed the prevalence and profile of treatment-related toxicities, with hematological toxicities being the most prevalent

Keywords

- acute lymphoblastic leukemia
- lymphoma
- induction chemotherapy
- treatment delay
- resource-limited settings

DOI https://doi.org/10.1055/s-0045-1811561.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

and infections and treatment delays being major concerns. High-risk disease was associated with increased toxicity, reinforcing the importance of proactive management strategies.

Introduction

Acute lymphoblastic leukemia (ALL) was earlier considered a highly fatal disease attributed to disease progression and relapse, necessitating intensive chemotherapy. With the invention of aggressive chemotherapy, the overall survival rates increased; disease- and relapse-related mortality came down; however, toxicity-related mortality (TRM) increased. To overcome this came the concept of risk-adapted therapy, which provides treatment based on risk stratification and minimal residual disease (MRD) analysis, to lessen the burden of treatment-related complications and mortality without compromising the efficacy of therapy. While advancements in risk-adapted therapy, molecular diagnostics, and supportive care have improved survival rates to over 80% in developed countries and 70% in India,[1] treatment-related toxicity (TRT) remains a major challenge.

Incidence of TRM in developed countries is $< 3\%$, but in developing countries like India, TRM ranges between 10% and 23%, with infections being the leading cause of TRM.[2] TRM during induction ranges between 8.6% and 10.6%.[2] TRM is just a tip of the iceberg.

Challenges in treating childhood ALL in India include treatment-related complications, lack of risk-adapted protocols, infrastructure limitations, delayed diagnosis, poor chemotherapy tolerance, and malnutrition.[3] Implementing risk-stratified therapy, early diagnosis, and adequate supportive care can mitigate these risks. Recent protocols including the Indian Collaborative Childhood Leukemia (ICiCLe) protocol now provide tailored therapy utilizing disease genetics and MRD analysis to improve outcomes, while minimizing toxicity and costs.[4]

Although toxicity profiles of chemotherapy regimens in ALL are well-studied in Western population, they may not be directly applicable to developing countries due to differences in socioeconomic factors, nutritional status, and prognostic factors.[2,3] The incidence and profile of TRT, not amounting to mortality, is not studied in detail from developing countries, which is essential for early intervention and improved management. Limited data exists on TRTs in Indian children, particularly in South India. This study aims to evaluate the toxicity profile in children with ALL/T-LL receiving induction chemotherapy at a tertiary care center in South India.

Materials and Methods

Study Design and Settings

This was a prospective cohort study conducted in a tertiary care center in South India between July 2022 and June 2024.

Sample Size

Considering a reported 20% toxicity rate during induction chemotherapy in ALL,[5] a sample size of 130 was calculated for 7% absolute precision; with 5% attrition, the final estimated sample size was 136.

Primary Objective

To determine the proportion of children developing TRT during induction chemotherapy for ALL/T-LL aged 1 month to 15 years.

Secondary Objectives

In children with ALL/T-LL aged 1 month to 15 years during induction chemotherapy,

- To study the cumulative duration and frequency of treatment delays and treatment protocol modification.
- To study the proportion of mortality in the study cohort.

Inclusion Criteria

All consecutive children aged 1 month to 15 years with newly diagnosed ALL/T-LL who are admitted for induction chemotherapy.

Exclusion Criteria

- Children who expired prior to initiation of induction chemotherapy due to disease-related complications.
- Those who left against medical advice prior to or during induction chemotherapy.

Expected Outcomes

Primary Outcome

The primary outcome of the study was the proportion of children with ALL/T-LL developing grade 3 or higher TRT during induction chemotherapy.

Secondary Outcomes

The secondary outcomes included:

1. Induction mortality rate
2. Cumulative duration and frequency of treatment delays during induction chemotherapy
3. Proportion of children requiring protocol modifications during induction chemotherapy
4. Association between risk group and incidence of grade ≥ 3 toxicities

Patient demographics, clinical characteristics, and laboratory details at the time of admission for induction chemotherapy were documented using a structured proforma. The diagnosis of ALL/T-LL and risk stratification were based on

standardized protocols, incorporating peripheral blood and bone marrow examination, cerebrospinal fluid analysis, flow cytometry, cytogenetics, and molecular studies.

Key data collected included demographic details, clinical examination findings, anthropometric measurements, malignancy details, risk group, treatment protocol adapted, and drugs administered, including doses. Chemotherapy was administered according to the Berlin-Frankfurt-Munster-95 or ICiCLe protocols as decided by the medical oncology team. Investigations were performed and toxicities were managed, if any, as part of routine management.

Children were followed up at regular intervals (twice weekly) from diagnosis till the end of induction chemotherapy. TRTs were recorded, along with supportive care interventions such as transfusions and critical care support, if any. Relevant investigations, including hematological, radiological, microbiological, and biochemical tests, were systematically documented.

The treatment breaks, timing of these breaks, the reasons for the same, and treatment/protocol modifications were noted. Cumulative treatment breaks at the end of induction were collected. Response assessments at the end of induction chemotherapy were recorded by bone marrow examination and MRD analysis. All data were collected from inpatient hospital records to ensure comprehensive analysis and evaluation. In the children who expired, the cause of mortality was noted and contributing factors were studied.

The degree of organ dysfunction and other TRTs were defined and graded as per the Common Terminology Criteria for Adverse Events Version 5.[6] Proportion of children developing toxicity and toxicity profile were described. The possible risk factors for TRT and mortality were analyzed.

Statistical Analysis

Data analysis was performed using SPSS software version 22.0. Categorical variables were presented as frequencies and percentages. The normality of continuous data was assessed using the Kolmogorov–Smirnov test. For normally distributed continuous variables, mean and standard deviation were used, while nonnormally distributed variables were expressed as median with interquartile range (IQR). Categorical variables were analyzed using the chi-square test or Fisher's exact test as appropriate.

To compare continuous data at the beginning and end of the study, a paired Student's *t*-test was applied for normally distributed data, whereas the Wilcoxon signed-rank test was used for nonnormal data. Univariate regression analysis was performed to assess the associations between $\geq$ grade 3 nonhematological toxicities and potential risk factors.

Results

Baseline Characteristics of the Study Population

A total of 112 children were eligible for enrollment in the study and 11 were excluded as they refused treatment or opted for care from another center. One hundred and one children were included in the study, of which 64 (63.37%) were male and 37 (36.63%) were female. Median age of the study population at diagnosis was 6 years (IQR 3, 11). One child (1%) was <1 year, 69 (68.32%) were between 1 and 10 years, and 31 (30.68%) were >10 years old. Median duration of complaints was 15 days (IQR 7, 30). Examination at admission revealed bulky lymphadenopathy in 7 (6.93%), bulky liver in 41 (40.59%), bulky spleen in 26 (25.74%), and bulky liver as well as spleen in 21 (20.79%) children. Mediastinal mass was observed in 17 (16.83%), pleural disease in 3 (2.97%), and central nervous system (CNS) involvement by clinical examination was observed in 3 children (2.97%). However, testicular involvement was observed in none and there was no radiologically or cytologically demonstrable CNS disease. Risk stratification was done based on the clinical and laboratory characteristics at admission, day 8 prednisolone response, and cytogenetics into standard risk, intermediate/medium risk, and high risk in 24 (23.76%), 29 (28.71%), and 48 (47.52%) children, respectively.

Thirty-one children (30.69%) had total leukocyte count (TLC) of $>50\times10^3/\mu L$ at presentation. Among the bone marrow/peripheral blood cytogenetics analyzed, favorable cytogenetics was observed in 21 children (20.82%) and high-risk cytogenetics was observed in 7 (6.9%) children, which included *t*(9;22) in 5 (4.9%), and Mixed-lineage leukemia (MLL) rearrangement in 2 (1.9%). Prednisolone response assessment on day 8 was done for 95 children, of which 20 children (21.05%) were prednisolone poor responders. Bone marrow assessment for MRD on day 35 was done for 81 children, of which 28 (34.56%) were MRD positive. Among the children with MRD positivity, the following observations were noted: 23 (82.1%) had B-lymphoblastic leukemia (B-ALL) and 5 (17.8%) had T lymphoblastic leukemia (T-ALL). Seven children each (50%) belonged to standard risk and intermediate risk, and 14 (50%) belonged to high risk at admission. The median duration of hospital stay of these patients was 40 days (36–43).

Flow cytometric analysis of the bone marrow/peripheral blood revealed B-ALL in 77 (76.24%), T-ALL including Early T-cell precursor (ETP)-ALL in 19 (18.81%), T-LL in 4 (3.96%) children, and mixed phenotype acute leukemia (B-lymphoblastic and myeloid leukemia) in 1 (0.99%) child.

The median *z*-scores for weight, height/length, and body mass index at admission were -1.53 (-2.12, -0.81), -0.99 (-1.65, -0.15), and -1.26 (-2.36, -0.45), respectively. Number of children who were underweight, stunted, and malnourished at admission were 30 (29.7%), 19 (18.8%), and 34 (33.7%), respectively.

Primary Objective

In the population studied, there were a total of 696 toxicities recorded among 101 children, of which 418 (60.06%) were of grade 3 and above, which amounts to a mean of 4 toxicities per person. Number of grades 3, 4, and 5 toxicities, in decreasing trend were 231 (33.1%), 180 (25.8%), and 7 (1%), respectively. Since the outcome of interest was toxicities of grade 3 and above, the profile of those toxicities was studied in detail. From the system-wise description of toxicity profile, it is observed that 73.2% were hematological and 26.8% were nonhematological. The proportion of TRTs is

Table 1 Systemwise description of toxicity profile (≧ grade 3)

System involved	Grades 3–5, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)
Hematological	306 (73.2)	150 (49.02)	156 (50.98)	0 (0)
Infectious	27 (6.46)	17 (62.96)	5 (18.5)	5 (18.5)
Cardiovascular	26 (6.22)	24 (92.31)	2 (7.69)	0 (0)
Metabolic	22 (5.26)	13 (59.09)	7 (31.81)	2 (9.09)
Gastrointestinal	15 (3.59)	15 (100)	0 (0)	0 (0)
Renal	10 (2.39)	5 (50)	5 (50)	0 (0)
Hepatobiliary	7 (1.67)	5 (71.43)	2 (28.57)	0 (0)
Central nervous	5 (1.12)	2 (40)	3 (60)	0 (0)

summarized in ►**Table 1**. The description of toxicities affecting each organ system, including the individual toxicities observed, and their week-wise distribution during induction chemotherapy, is summarized in ►**Table 2**.

It is observed that majority of the hematological toxicities of higher grades occurred in week 1 as summarized in ►**Table 2**. A total of 59 febrile neutropenic events were recorded among 50 children. Of these, 42 children (84%) had B-ALL, 7 (14%) had T-ALL, and 1 (2%) had mixed phenotype. Based on clinical and laboratory criteria, these children were risk-stratified as follows: 7 (14%) in the standard-risk group, 19 (38%) in the intermediate-risk group, and 24 (48%) in the high-risk group. Nutritional assessment at admission revealed that 15 children (30%) were underweight, 10 (20%) were stunted, and 17 (34%) were wasted. Majority (32.2%) were observed in week 3, followed by week 2 (25.42%), and the least (5.08%) in week 5. The number of grade 3 and grade 4 febrile neutropenic events were 55 (93.2%) and 4 (6.8%), respectively. The median time to resolution of febrile neutropenic events was 3 days (IQR 1, 2).

Among the metabolic toxicities, tumor lysis syndrome (TLS) was the most common, seen in 17 children (73.9%), most of which occurred in week 1 (82.35%) with median time to resolution (for toxicities of grades 3 and 4) of 3 days (2–4). Of these, 9 children (52.9%) had B-ALL, 7 (41.1%) had T-ALL, and 1 (5.8%) had T-LL. These children were risk-stratified as follows: 1 (5.8%) in the standard-risk group, 3 (17.6%) in the intermediate-risk group, and 13 (76.4%) in the high-risk group. Nutritional assessment at admission revealed that 5 children (29.4%) were underweight, 2 (11.7%) were stunted, and 5 (29.4%) were wasted. TLS of grades 3, 4, and 5 were observed in 8 (47.06%), 7 (41.1%), and 2 (11.7%), respectively. Hyperglycemia was recorded in 3 children (13.1%), all older than 10 years, during weeks 1 and 2, treated with oral hypoglycemic agents and insulin, and median time to resolution noted was 15 days (12, 28). Hypertension was the only cardiovascular toxicity observed in the population studied with majority occurring in weeks 1 and 2 (30.77 and 34.61%, respectively) with median time to resolution of 14 days (10–20). The common gastrointestinal toxicities observed were diarrhea, chemo-induced nausea and vomiting (CINV), and oral mucositis, as described in ►**Table 2**, most of which occurred in week 2. The observed hepatoxicities include transaminitis and hyperbilirubinemia, which occurred in weeks 1 and 2.

The observed renal toxicities include acute kidney injury (AKI) in majority (80%), all of which are reported in week 1 and tubulopathy in the rest (20%), reported in weeks 3 and 4. According to the KDIGO (Kidney Disease: Improving Global Outcomes) criteria, stage 3 AKI was observed in 5 children (4.95%). There were 5 CNS toxicities reported; with seizures being the most common (40%) attributed to electrolyte imbalance.

Infectious Complications

Fifty-three infectious complications were observed in the cohort studied, which include both clinically and microbiologically documented infections. Of which 27 were of grade 3 and above, which include blood stream infections (BSIs) (55.5%), description of which is given in ►**Table 3**; soft tissue, gastrointestinal, and lower respiratory tract infections contribute to the rest (44.5%). The median time to resolution of BSI (of grades 3 and 4) was 10 days (8–14). The incidence of clinically documented infections (CDIs), microbiologically documented infections (MDI), BSI, and multiorgan dysfunction syndrome (MODS) is presented in ►**Table 3**. Culture-proven BSI were documented in 15 children (14.85%), of which 9 (8.91%) went into MODS/septic shock.

Secondary Objectives

A total of 9 mortalities were observed among the population studied (8.9%). The causes of mortality are listed in ►**Table 4**. Infection-related mortality was observed in 5 children (55.5%). Risk factors associated with mortality could not be analyzed in this study as the event rate was less and hence could not be compared with the rest of the population studied. However, among this population, majority (77.8%) belonged to the high risk, 44.4% expired in week 1 of illness, and one had Downs phenotype.

Out of the 101 children studied, treatment delay was observed in 51 children (50.49%) during the study period; of which 37 (72.5%) had single treatment break and 14 (27.45%) had treatment breaks in two separate occasions. Hence, a total of 65 treatment breaks were observed and the total number of days in breaks was 294, which accounts for a mean

Table 2 Profile of aforementioned toxicities

	Toxicity	Number of toxicities analyzed *n* (%)	Week 1 *n* (%)	Week 2 *n* (%)	Week 3 *n* (%)	Week 4 *n* (%)	Week 5 *n* (%)
1	Hematological ($n = 306$)						
	Anemia	84 (27.45)	74 (88.1)	5 (5.95)	2 (2.38)	3 (3.57)	0 (0)
	Neutropenia	85 (27.78)	24 (28.23)	16 (18.82)	41 (48.23)	4 (4.72)	0 (0)
	Thrombocytopenia	78 (25.49)	53 (67.95)	13 (16.67)	11 (14.1)	1 (1.28)	0 (0)
	Febrile neutropenia	59 (19.28)	13 (22.04)	15 (25.42)	19 (32.20)	9 (15.25)	3 (5.08)
2	Infectious ($n = 15$)						
	BSI	15	3 (20)	3 (20)	4 (26.6)	4 (26.6)	1 (6.7)
3	Metabolic ($n = 22$)						
	TLS	17 (73.9)	14 (82.35)	3 (17.65)	0 (0)	0 (0)	0 (0)
	Hyperglycemia	3 (13.1)	2 (66.67)	1 (33.33)	0 (0)	0 (0)	0 (0)
	Hypocalcemia	1 (8.7)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
	Hypokalemia	1 (4.3)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
4	Cardiovascular ($n = 26$)						
	Hypertension	26	8 (30.77)	9 (34.61)	5 (19.23)	4 (15.39)	0 (0)
5	Gastrointestinal ($n = 22$)						
	Diarrhea	4 (18.18)	0 (0)	2 (50)	0 (0)	2 (50)	0 (0)
	Transaminitis	4 (18.18)	2 (50)	2 (50)	0 (0)	0 (0)	0 (0)
	Hyperbilirubinemia	3 (13.63)	1 (33.33)	2 (66.67)	0 (0)	0 (0)	0 (0)
	CINV	3 (13.64)	1 (33.33)	2 (66.67)	0 (0)	0 (0)	0 (0)
	Oral mucositis	3 (13.63)	0 (0)	1 (33.33)	1 (33.33)	1 (33.33)	0 (0)
	Ileus	2 (9.09)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)
	Pancreatitis	2 (9.09)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)
	Gastritis	1 (4.54)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
6	Renal ($n = 10$)						
	AKI	8 (80)	8 (100)	0 (0)	0 (0)	0 (0)	0 (0)
	Tubulopathy	2 (20)	0 (0)	0 (0)	1 (50)	1 (50)	0 (0)
7	Central nervous system ($n = 5$)						
	Seizure	2 (40)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)
	PRES	1 (20)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
	Leukoencephalopathy	1 (20)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
	Traumatic myelopathy	1 (20)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)

Abbreviations: AKI, acute kidney injury; BSI, blood stream infections; CINV, chemotherapy-induced nausea and vomiting; PRES, posterior reversible encephalopathy syndrome; TLS, tumor lysis syndrome.

delay of 5.76 days per person. Maximum number of treatment interruptions were observed in week 3 (33.9%), followed by week 2 (27.7%), week 4 (20%), week 1 (16.9%), and week 5 (1.5%). It is observed that majority of treatment interruptions (75.38%) were due to febrile neutropenia (44.6%) and infection-related (CDI 15.38% and MDI 15.38%). The rest were due to hepatotoxicity (7.69%), CINV (4.61%), suspected pancreatitis (6.15%), ileus (4.61%), and seizures (1.53%). Treatment/protocol modification was observed in 10 (9.9%); of which protocol modification was observed in 4 (36.3%) children (high risk to intermediate risk in 3 and to standard risk in 1); chemotherapeutic agent dose reduction was seen in 5 children (49.5%), both owing to excessive toxicities, and alternate chemotherapeutic agent was used in 1 child (9.2%) with CNS metastasis.

A statistically significant association was observed between risk group and nonhematological toxicities of grade $\geq$ 3, with the nonstandard risk group (intermediate- and high-risk groups) exhibiting 3.21 times higher odds of experiencing these toxicities compared with the standard-risk

Table 3 Incidence of CDI, MDI, and sepsis

S. no.	Infections	$N = 101$ *n* (%)
1	**CDI**[a]	**24 (23.76)**
	• Upper respiratory tract infections	9 (37.5)
	• Gastrointestinal infections	7 (29.2)
	• Oral infections	4 (16.6)
	• Lower respiratory tract infections	3 (12.5)
	• Soft tissue infection	1 (4.2)
2	**MDI**[b]	**29 (28.7)**
	• **Blood stream infections**	**15 (51.7)**
	Bacterial	
	MSSA[c]	3 (20)
	Pseudomonas aeruginosa	2 (13.33)
	Escherichia coli	2 (13.33)
	Salmonella enterica	2 (13.33)
	Klebsiella pneumoniae	1 (6.66)
	MRSA[d]	1 (6.66)
	Streptococcus dysgalactiae	1 (6.66)
	Fungal	
	Candida albicans	2 (13.33)
	Trichosporon azaki	1 (6.66)
	• **Upper respiratory tract infections**	**8 (27.58)**
	RSV[e]	3 (37.5)
	Influenza	5 (62.5)
	• LRI[f]- Pulmonary aspergillosis	2 (6.89)
	• **Soft tissue infections**	**2 (6.89)**
	MSSA[c]	1 (50)
	MRSA[d]	1 (50)
	• UTI[g] (Klebsiella)	1 (3.44)
	• Otitis media (Pseudomonas aeruginosa)	1 (3.44)
3	**Septic shock/MODS**[h]	**9 (8.91)**

[a] CDI, Clinically documented infection; [b] MDI, Microbiologically documented infection; [c] MSSA, Methicillin sensitive Staphylococcus aureus; [d] MRSA, Methicillin resistant Staphylococcus aureus; [e] RSV, Respiratory syncytial virus; [f] LRI, lower respiratory tract infection; [g] UTI, urinary tract infection; [h] MODS, Multiorgan dysfunction syndrome.
Note: Boldfaced values indicate the proportion of the main group, with the corresponding subgroup proportions presented in the same cell.

group with a *p*-value of 0.022 (95% confidence interval [CI] 1.18–8.71) (►**Table 5**). As only one factor was found to be statistically significant, multivariable regression analysis was not performed.

Discussion

In this observational cohort study, we prospectively analyzed TRTs of ≥ grade 3 in children aged 1 month to 15 years with ALL/T-LL undergoing induction chemotherapy. We reported their incidence, profile and timing, assessed risk factors associated with these TRT, along with treatment delays, and outcomes in terms of mortality and MRD status.

Toxicities

Among the toxicities observed, 60% were ≥ grade 3 and only those were analyzed due to clinical relevance. The incidence of grade 3, 4, and 5 toxicities was 33.91%, 25%, and 1%, respectively, compared with 32.1%, 16%, and 4.5% in another study.[7] The most common toxicity observed was hematological (73.2%), significantly higher than the 45.8% reported in a Mexican study.[7] A total of 169 nonhematological toxicities ≥ grade 3 were observed in 77 children (mean: 2.19 toxicities/person). Several studies report 40% of ALL children experiencing ≥ 1 TRT.[8]

Hematological Toxicities

Anemia, neutropenia, and thrombocytopenia ≥ grade 3 occurred in 27.45%, 27.78%, and 25.49%, respectively, of our study population; Ozdemir et al reported higher incidence of 34%, 51% (≧ grade 3 anemia and thrombocytopenia, respectively), and 60% (grade 4 neutropenia).[9] Febrile neutropenia accounted for 19.28% of hematological toxicities and 14.11% of all ≥ grade 3 toxicities.

Nonhematological Toxicities

In a retrospective analysis done by Zawitkowska et al on grade 3 and 4 toxicities, the common nonhematological toxicities reported were infectious in 32.3%, hepatic in 28.2%, gastrointestinal in 20.64%, followed by the less

Table 4 Risk factors and causes of mortality

S. no.	Age (y)	Gender	Risk group	Immunophenotype	Day of outcome	Cause of mortality
1	14	Male	HR	T-ALL	23	Septic shock
2	11	Male	HR	B-ALL	6	TLS- hyperkalemia
3	4	Male	HR	T-ALL	6	Intracranial hemorrhage
4	13	Female	IR	B-ALL	35	Septic shock
5	15	Male	HR	B-ALL	7	Septic shock
6	4	Female	HR	B-ALL	20	Septic shock
7	13	Male	HR	T-ALL	8	CNS metastasis- Raised ICP
8	5	Female	IR	B-ALL	8	Septic shock
9	13	Male	HR	B-ALL	7	TLS- AKI

Abbreviations: AKI, acute kidney injury; B-ALL, B-lymphoblastic leukemia; CNS, central nervous system; HR, high risk; ICP, intracranial pressure; IR, intermediate risk; T-ALL, T-lymphoblastic leukemia; TLS, tumor lysis syndrome.

Table 5 Univariate analysis of the risk factors associated with nonhematological toxicities of grades 3 and above among the study population

Characteristics	Total	Toxicity present *n* (%)	No toxicity *n* (%)	Unadjusted risk ratio (95% CI)	*p*-Value
Age					
1–10 y	69	52 (75.40)	17 (24.6)	–	0.76
< 1 y or > 10 y	32	25 (78.1)	7 (21.9)	1.16 (0.43–3.17)	
Gender					
Male	64	47 (73)	17 (27)	–	0.387
Female	37	30 (81.1)	7 (18.9)	1.55 (0.57–4.18)	
Risk group					
Standard risk	24	14 (58.3)	10 (41.7)	–	0.022
Nonstandard risk	77	63 (81.8)	14 (18.2)	3.21 (1.18–8.71)	
Protocol followed					
ICiCLe	84	65 (77.4)	19 (22.6)	–	0.55
BFM-95	17	12 (70.6)	5 (29.4)	0.71 (0.22–2.24)	
Flow cytometry					
B-ALL	78	62 (79.5)	16 (20.5)	–	0.163
T-ALL	23	15 (65.2)	8 (34.8)	0.48 (0.17–1.34)	
Underweight and severe underweight at admission (< 2 *z*-score)					
No	71	54 (76.1)	17 (23.9)	–	0.947
Yes	30	23 (76.7)	7 (23.3)	1.03 (0.37–2.83)	
Stunting and severe stunting at admission (< 2 *z*-score)					
No	84	66 (78.6)	18 (21.4)	–	0.226
Yes	17	11 (64.7)	6 (35.3)	0.5 (0.16–1.53)	
Thinness and severe thinness at admission (< 2 *z*-score)					
No	67	51 (76.1)	16 (23.9)	–	0.969
Yes	34	26 (76.5)	8 (23.5)	1.02 (0.38–2.69)	

Abbreviations: B-ALL, B-lymphoblastic leukemia; BFM-95, Berlin-Frankfurt-Munster-95; CI, confidence interval; ICiCLe, Indian Collaborative Childhood Leukemia group; T-ALL, T-lymphoblastic leukemia.

common toxicities, CNS, cardiac, and renal and skeletal in 2.9%, 2.7%, and 1.5%, respectively.[5] Studies by Stary et al and Demidowicz et al also reported similar system-wise toxicities.[10,11] A Mexican study reported induction chemotherapy toxicities in 81.2% of children (mean: 2 toxicities/person), with febrile neutropenia (18.8%), allergic reactions (6.3%), and sepsis (6%) being common.[7] In our study, infections were predominant among nonhematological toxicities, but gastrointestinal and hepatic toxicities were substantially lower.

Infections comprised 6.46% of all toxicities, with BSI being the most common (14.85%). Reported infection rates in other studies range from 25% to 58%.[7,12] In a study done in Taiwan, fever was reported to occur at any point in 86.9%, febrile neutropenia was observed in 64%, CDI in 39%, and MDI in 44%.[13] The magnitude of infectious toxicities in other studies was substantially higher compared with our study, which could probably be due to differences in the characteristics of the study population, protocols used, and with those being studied at different phases of chemotherapy.

Our study reported febrile neutropenia in 19% and MODS/septic shock in 9%, lower than the 10% to 19% reported in another South Indian study by Rajeswari et al.[14] BSIs were mostly monomicrobial, unlike Brazilian studies reporting polymicrobial infections (6%). Our fungal sepsis rate (20%) was considerably higher than the reported 4.7%.[15]

Gastrointestinal toxicities (≥ grade 3) occurred in 3.59% of our study population, including diarrhea (0.9%), mucositis (0.7%), CINV (0.7%), and pancreatitis (0.5%). Literature reports higher rates of gastrointestinal toxicities accounting for 20.4%[5]; with mucositis (5%), CINV and, diarrhea (6%) during induction,[7] and pancreatitis (5–10%).[16] Age > 10 years, genetic predisposition, and presence of hypertriglyceridemia were observed risk factors for pancreatitis by Hough and Vora.[17] Hepatotoxicity was observed in 1.67%, significantly lower than reported rates of 15.6 to 28%.[18,19]

Hyperglycemia ($\geq$ grade 3) was seen in 2.97% of cases, lower than the 10% to 20% reported in literature.[20] TLS occurred in 16.8% of cases, with clinical TLS in 8.9%, significantly lower than the reported 45% to 62%.[21] Hyperuricemia and hyperphosphatemia were the most common biochemical abnormalities reported in our study consistent with the literature.[21] Lower incidence in our study could be due to prophylactic measures including aggressive hydration, use of xanthine oxidase inhibitor (allopurinol) and better monitoring. Our study found hypertension in 6.2% of cases, lower than literature-reported rates (13–17.8%).[19] Renal toxicity was observed in 2.39%, with AKI in 7.9% and tubulopathy in 2%, lower than literature-reported 14% and 12.5%, respectively.[19,21]

Neurological toxicities were rare (1.12%), including seizures, posterior reversible encephalopathy syndrome, and myelopathy. Seizure incidence (2%) was much lower than the reported 10% to 15%.[19] Literature reports neurotoxicity in 3.6%, mostly during induction, including methotrexate-induced leukoencephalopathy (35.4%) and vincristine-induced vocal cord paralysis (14%).[22] We observed one case of methotrexate-induced leukoencephalopathy and one of traumatic myelopathy post-intrathecal methotrexate.

Treatment Delays

TRTs often led to treatment modifications and delays, potentially impacting treatment efficacy. In our study, delays were observed in 50.49% of children. Yeoh et al reported neutropenia (33%), febrile neutropenia (19%), and severe infections (19%) as the reasons for treatment delay, which is on par with our study.[23] Li et al reported delays due to infections in 7% of children, with a higher median duration of 8 days.[24] Ozdemir et al found that delays before day 8 increased mortality risk by 30%, especially in high-risk groups.[9] In our study, 16.9% of breaks occurred in the first week, peaking to 33% in week 3. Hence, attempts should be made to reduce treatment breaks anticipating toxicities during mid-weeks of induction.

Among 51 (50.4%) children with treatment delay, induction outcome in terms of MRD status are as follows: 37 (36.6%) were MRD negative, 9 (8.9%) were positive, and analysis could not be done in 5 children (4.9%) ►**Supplementary Table S1**. These findings suggest that short-term treatment delays during induction may not uniformly lead to poor MRD outcomes and could be influenced by underlying disease biology, early response to therapy, and these results could possibly be due to selection bias/confounding factors resulting in skewing. However, the unexpected MRD response in children with treatment delays warrants further investigation through larger, prospective studies.

Mortality

Induction mortality in developed countries ranges from 1% to 2.8%,[10,25–27] with infections (72%) and bleeding/thrombosis (9%) as leading causes.[16] In developing countries, TRM ranges from 10% to 29% with majority due to infections and bleeding.[2,28,29] Mortality outcomes from our study reveal that the incidence of induction mortality tends to be higher compared with developed countries and lower compared with developing countries; however, the causation seems to be comparable. These findings highlight the need for enhanced supportive care, early initiation of antimicrobial therapy, guideline-based platelet transfusions, and improved health care accessibility. Predictive risk factors for induction mortality include female gender, Down syndrome, high-risk disease (odds ratio [OR] 1.84), high initial TLC (OR 1.02), low initial platelet count, and long travel time to health care facilities (OR 1.06/hour).[16,30] However, due to a low event rate, these associations could not be analyzed in our study.

Risk Factors for Toxicities

Both genetic and acquired factors influence TRM and individual toxicities. Studies highlight age, gender, immunophenotype, risk group, chemotherapy intensity, and day 33 remission status as significant factors. Older age and T-ALL are independent risk factors for toxicities, with incidence increasing from 44.5% (1–9 years) to 57.6% (10–14 years).[25] Older children have higher risks of developing pancreatitis, hepatotoxicity, hyperglycemia, and methotrexate-induced neutrotoxicity.[16] Meeske et al found female gender to be associated with increased grades 3 to 5 toxicities, treatment delays, infections, increased hospital stay, and supportive care requirements, as well as higher TRM risk.[31] Nonstandard risk groups had significantly higher toxicity risk (OR 3.21 [95% CI: 1.18–8.71], $p = 0.022$) in our study. However, no associations were found between age, gender, immunophenotype, and increased toxicity risk.

This prospective study provides valuable real-time data on TRTs during induction chemotherapy in children with ALL/T-LL in a resource-limited setting, using standardized criteria. This study offers granular, week-wise data on both hematological and nonhematological toxicities, highlighting peak periods and duration of specific toxicities, that can guide targeted supportive care. This single-center design limits generalizability and as this was limited to the induction phase, long-term and cumulative toxicities could not be assessed. While these results are particularly relevant to similar low- and middle-income settings, a more detailed subanalysis of specific toxicities stratified by each risk factor would indeed offer additional insights. Future multicenter studies with longer follow-up, evaluation of nutritional status, and supportive interventions are needed to better understand and mitigate these toxicities, and should focus on optimizing supportive care interventions and identifying biomarkers predictive of severe toxicities to further improve outcomes in pediatric ALL.

Conclusion

Our study provides critical insights into TRTs during induction chemotherapy in pediatric ALL. While hematological toxicities were predominant, infectious complications, though lower than in other studies, remained a notable concern. Treatment delays were frequent, peaking in week 3. Mortality rates were lower than in developing countries but higher than in developed nations, emphasizing the need

for improved supportive care. High-risk disease was associated with increased toxicity, reinforcing the importance of personalized risk stratification and proactive management strategies. Future multicenter research with long-term follow-up should aim to evaluate nutritional status, refine supportive care measures, and identify early predictors of severe toxicities to improve treatment outcomes in children with ALL.

Authors' Contributions

M.S. and J.G.R. conceptualized the study, collected data, analyzed data, and prepared the manuscript. J.G.R. supervised the study, critically revised the manuscript, and act as a guarantor of the paper. The manuscript has been read and approved by all the authors and the requirements for authorship have been met. Each author believes that the manuscript represents honest work, and the information is provided in original form.

Ethical Approval

The study was approved by the Institutional Ethics Committee and the approval certificate numbered JIP/IEC/2022/151 dated 13.07.2022 was issued. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013).

Patient Consent

Written informed consent was obtained from the parents or legally acceptable representatives of the participants and assent was obtained from the participants wherever applicable.

Funding

None.

Conflict of Interest

None declared.

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