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FACTORS AFFECTING OUTCOME OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA FOLLOWING INDUCTION CHEMOTHERAPY – A PROSPECTIVE OBSERVATIONAL STUDY FROM CENTRAL INDIA

Oncology

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ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, peaking between 2 and 5 years of age. Induction chemotherapy is essential for achieving remission but is associated with complications such as febrile neutropenia, mucositis, and sepsis. This study assesses the impact of nutritional status on treatment outcomes, complications, and mortality in children with ALL undergoing induction chemotherapy in a tertiary care cancer center in Central India. **Materials and Methods:** This prospective, observational cohort study was conducted between February 2023 and August 2024 at a tertiary care cancer institute in Central India. Children under 18 years diagnosed with ALL and treated according to the Berlin-Frankfurt-Münster (BFM)-2002 protocol were included. Data on demographics, clinical presentation, laboratory parameters, and treatment outcomes were collected. The primary outcomes analyzed were induction chemotherapy duration, febrile neutropenia episodes, drug-related toxicities, tumor lysis syndrome, and mortality. Statistical significance was set at $p < 0.01$ using chi-square and t-tests. **Results:** Among 69 children, 39 (56.5%) were male and 30 (43.5%) females. Age distribution showed 30% under five years, 54% between 5-10 years, and 16% over ten years. Malnourished children had significantly prolonged chemotherapy duration ($p < 0.01$), more febrile episodes, increased infectious complications, and a higher incidence of prolonged neutropenia ($p < 0.01$). The overall induction mortality rate was 16%, with sepsis due to prolonged neutropenia being the leading cause of death. **Conclusion:** Nutritional status critically affects treatment outcomes in children with ALL. Routine nutritional assessment and supplementation, coupled with infection control, may improve survival in resource-limited settings. These findings emphasize the need to integrate nutritional support into ALL treatment protocols, especially in low- and middle-income countries, to enhance patient survival and quality of life.

KEYWORDS

Acute Leukemia, Pediatric patients, Induction chemotherapy

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Its incidence peaks between the ages of 2 and 5, and in recent decades, survival rates for children diagnosed with ALL have improved dramatically, with a current survival rate of about 90% in developed countries[1,2]. This remarkable achievement has been made possible due to advances in early diagnosis, risk stratification, and treatment protocols, especially the use of intensive, multi-agent chemotherapy regimens such as the Berlin-Frankfurt-Münster (BFM) protocol.

To properly risk stratify a child with ALL, it is essential to identify the structural mutations of the chromosomes. The World Health Organization (WHO) classifies B-cell ALL based on molecular analysis and cytogenetics. Cytogenetic classifications include aneuploidy, with high-hyperdiploidy (chromosome number ≥51) and hypodiploidy (chromosome number ≤44). Common translocations seen in ALL include t (12;21) with ETV6-RUNX1, t(1;19) with TCF3-PBX1, t(9;22) with BCR-ABL1, and KMT2A rearrangement[3,4,5].

The treatment of ALL in children involves multiple phases, with induction chemotherapy being the first and most critical stage[6]. The goal of induction therapy is to achieve complete remission (CR), defined as the elimination of leukemic cells from the bone marrow and blood. However, the intensity of chemotherapy during this phase is associated with significant toxicities, including febrile neutropenia, mucositis, infections, and tumor lysis syndrome, all of which can complicate treatment and impact survival rates.

Moreover, in resource-limited settings like India, malnutrition is a prevalent issue among children. It is well established that malnutrition can impair immune function, reduce tolerance to chemotherapy, and increase the risk of infections. Therefore, malnourished children are more susceptible to treatment-related complications, which can adversely affect their prognosis.

The primary objective of this study was to analyze the clinical presentation, complications, and outcomes of children with ALL during the induction phase of chemotherapy at our center. Additionally, we aimed to assess the impact of nutritional status on the duration of induction, frequency of febrile episodes, and mortality.

MATERIALS AND METHODS

Study Design

This study was a prospective, observational cohort study conducted at a tertiary care cancer institute in Central India. It included children under 18 years of age diagnosed with ALL, who were admitted to the pediatric oncology ward of the institution between February 2023 and August 2024.

Inclusion Criteria

Children under the age of 18 years who were newly diagnosed with ALL and received induction chemotherapy according to the BFM-2002 protocol were eligible to participate in the study. Informed consent was obtained from the guardians or parents of the patients.

Exclusion Criteria

Patients with secondary malignancies, relapsed ALL, or those who did not complete induction chemotherapy for reasons other than death were excluded from the analysis.

Data Collection

Data were collected from medical records, including detailed demographic information, clinical presentation, laboratory investigations, and treatment details. The outcomes evaluated at the end of the induction phase included:

1. Number of episodes of febrile neutropenia.
2. Drug-related toxicities such as mucositis, vomiting, and neutropenic enterocolitis.
3. Tumor lysis syndrome and other complications.
4. Mortality during the induction phase, with specific attention to causes of death.

Special emphasis was placed on the nutritional status of the children at the time of diagnosis. The children were categorized as malnourished or well-nourished based on Body mass index (BMI).

Statistical Analysis

Data were analyzed using standard statistical software. Chi-square and t-tests were employed to determine the significance of various factors affecting outcomes. A p-value of less than 0.01 was considered statistically significant.

RESULTS

The study presents data (Refer to Table 1) on a cohort of pediatric patients diagnosed with Acute Lymphoblastic Leukemia (ALL), analysing their demographic features, clinical presentation, molecular characteristics, complications, and outcomes.

The median age of the patients was 6.4 years, with an age range of 6 to 16 years. There was a notable gender imbalance, with a male-to-female ratio of 1:3, indicating a predominance of female patients.

Patients exhibited a range of symptoms at presentation. Fever was the most common symptom, observed in 56% of cases, followed by hepatosplenomegaly in 67% of patients. Rash was present in 40%, while bleeding manifestations were noted in 30%.

Patients were categorized into different risk groups based on disease severity and prognostic markers. Most patients fell into the intermediate-risk category (56.5%), followed by the standard-risk group (23%), while 20% were classified as high-risk.

Among molecular markers, the BCR-ABL minor transcript was detected in 5% of patients, whereas MLL rearrangements were present in 2.8%. No cases of hyperdiploidy or hypodiploidy were reported.

Immunophenotypic aberrancies were observed in 20% of B-cell ALL cases and 36% of T-cell ALL cases. In total, 23% of patients exhibited aberrant immunophenotypic features.

Table 1: Patient Characteristics

	Parameters	No (%)
Age in years	Median age	6.4years (6-16)
Sex	Male: Female	01:03
Clinical Presentation	Fever	39 (56)
	Rash	27 (40)
	Hepato-splenomegaly	46 (67)
	Bleeding	21 (30)
	Severe Malnutrition (BMI <3rd centile)	28 (20)
Type of ALL	B-cell	58(94%)
	T-cell	11(16%)
	Mixed	None
Risk stratification	Standard	16(23)
	Intermediate	39(56.5)
	High	14(20)
Molecular/	BCR-ABL minor transcript	4(5%)
Karyotype	MLL rearrangements	2(2.8%)
	Hyper or hypodiploidy	None
Aberrancy	B cell ALL	12 (20)
	T cell ALL	4 (36)
	Total	16 (23)
Complications during induction	Febrile neutropenia	46(68)
	Vomiting	15(22)
	Mucositis	21(30)
	Neutropenic enterocolitis	7(10)
	Tumor lysis syndrome.	8912)
Mortality	B cell ALL	8 (13.7)
	T Cell ALL	3(27.2)

Complications During Induction Therapy

Induction therapy was associated with several complications. Febrile neutropenia was the most common, affecting 68% of patients. Mucositis was observed in 30%, vomiting in 22%, and neutropenic enterocolitis in 10%. Additionally, 12% of patients developed tumor lysis syndrome.

The overall mortality rate was 16%. The mortality rate among B-cell ALL patients was 13.7%, while it was significantly higher among T-cell ALL patients at 27.2%.

Impact of Clinical Complications on Survival

Fever was a common symptom, present in 52 patients (42 survivors and 10 deceased). The absence of fever was observed in 6 patients, all of whom survived. However, the difference between groups was not statistically significant ($p = 0.577$), indicating that fever alone did not significantly impact mortality.

Undernutrition (BMI <5th percentile) was a critical factor affecting survival. Among the 30 malnourished patients, 9 died, while only 1 death occurred among the 39 well-nourished children. This association was statistically significant ($p = 0.001$), suggesting that poor nutritional status substantially increased the risk of mortality.

Severe Mucositis (Common Terminology Criteria for Adverse Events Grade III or Higher was another significant risk factor. Among the 25 patients with Grade III or higher mucositis, 9 died, while only 1 death occurred among the 34 patients without severe mucositis. The statistical significance ($p = 0.001$) underscores the association between severe mucositis and increased mortality, potentially due to infection risk and treatment delays.

Febrile neutropenia was observed in 45 patients, of whom 36 survived and 9 died. However, this difference was not statistically significant ($p = 0.429$), indicating that febrile neutropenia alone was not a strong predictor of mortality.

Neutropenic enterocolitis, a severe gastrointestinal complication, was present in 15 patients. Of these, 14 survived, while only 1 patient died. However, 9 out of 44 patients without enterocolitis died, suggesting no significant association between this complication and mortality ($p = 0.427$).

Tumor Lysis Syndrome (TLS) was observed in 9 patients, with 6 survivors and 3 deceased. Among the 49 patients without TLS, 42 survived and 7 died. Although TLS was associated with a higher mortality rate, this finding was not statistically significant ($p = 0.177$).

Table 2 : Factors Affecting Outcome of Children with ALL

Patient characteristic	Outcome		Fischer Exact Value df p value
	Alive (n=49)	Dead (n=10)	
Molecular analysis			
None	44	9	5.636 3 0.131
t (9:22)	3	0	
t(4:11)	0	1	
t(1:19)	1	0	
Complications			
Febrile neutropenia Present (52)	42	10	1.394 1 0.577
Undernutrition (BMI <5 centile) Present (30) \	21	9	10.836 1 0.001
Mucositis (Grade III or more) Present (25)	16	9	10.836 1 0.001
Febrile Neutropenia Present (45)	36	9	1.071 1 0.429
Neutropenic enterocolitis Present (15)	14	1	1.586 1 0.427
Tumor Lysis Syndrome Present (9)	6	3	1.933 1 0.177

DISCUSSION

Acute Lymphoblastic Leukemia (ALL) remains the most common pediatric malignancy, and despite advancements in treatment, outcomes are influenced by multiple factors, including clinical presentation, molecular characteristics, risk stratification, and treatment-related complications. This discussion evaluates the findings from our study in the context of existing literature to provide insights into the prognosis and factors affecting survival in pediatric ALL patients.

Clinical Presentation and Risk Stratification

In our cohort, the median age of presentation was 6.4 years, with a female predominance (male-to-female ratio of 1:3). This aligns with previous studies indicating a peak incidence of ALL between 2 and 6 years of age, though global epidemiological trends show a male predominance[7] (Hunger et al., 2012). Clinical symptoms such as fever (56%) and hepatosplenomegaly (67%) were common, consistent with findings from Steliarova-Foucher et al. (2018), who reported that constitutional symptoms and organomegaly are primary indicators of leukemia at diagnosis[8].

Risk stratification is a crucial determinant of treatment intensity. In our study, 56.5% of patients were classified as intermediate-risk, 23% as standard-risk, and 20% as high-risk. The predominance of the intermediate-risk category is similar to findings by Pui et al. (2019), where risk-adapted therapy has led to improved survival rates. However, high-risk patients continue to have inferior outcomes, necessitating novel therapeutic strategies[9].

Molecular and Cytogenetic Abnormalities

Molecular markers play a critical role in prognosis. BCR-ABL minor transcript (Philadelphia chromosome) was detected in 5% of cases, a figure consistent with rates reported by Aricò et al. (2010), where BCR-ABL positivity was associated with poor prognosis unless treated with tyrosine kinase inhibitors[10]. MLL rearrangements were found in 2.8% of cases, a frequency slightly lower than the reported 5–10% incidence in pediatric ALL (Pui et al., 2019). The absence of hyperdiploidy, a favorable prognostic marker, suggests that our cohort had a more aggressive disease profile.

Impact of Treatment-Related Complications

Induction chemotherapy is associated with several toxicities. Febrile neutropenia was the most common complication (68%), followed by mucositis (30%), vomiting (22%), and tumor lysis syndrome (12%). Febrile neutropenia rates in our study are comparable to those reported by Sung et al. (2013), where febrile neutropenia occurred in 60–70% of pediatric ALL patients, significantly impacting morbidity. Mucositis (Grade III or higher) was significantly associated with mortality (p=0.001), similar to findings by Sonis et al. (2004), who reported that severe mucositis increases the risk of bloodstream infections and delays treatment, negatively affecting survival[11].

Nutritional Status and Survival

Undernutrition, defined as BMI below the 5th percentile, was significantly associated with mortality (p=0.001). Malnutrition in children with ALL has been widely recognized as a negative prognostic factor. A study by Sala et al. (2012) reported that malnourished children with ALL had a twofold higher risk of mortality compared to well-nourished patients[12], likely due to impaired immune function and poor tolerance to chemotherapy. Our findings reinforce the importance of nutritional interventions in ALL management.

Mortality and Prognostic Factors

Overall, 16% of patients succumbed to the disease, with a higher mortality rate in T-cell ALL (27.2%) compared to B-cell ALL (13.7%). This aligns with data from Bhojwani and Pui (2013), who noted that T-cell ALL has historically been associated with inferior survival, although intensified chemotherapy regimens have improved outcomes[13]. Our study also demonstrated that the presence of mucositis and undernutrition were the most significant predictors of mortality.

Conclusion and Future Directions

Our study highlights key factors affecting survival in pediatric ALL, including risk stratification, molecular abnormalities, treatment-related toxicities, and nutritional status. The findings underscore the need for early nutritional interventions, aggressive management of treatment-related complications, and targeted therapies for high-risk molecular subtypes. Future research should focus on novel immunotherapies, supportive care measures, and personalized treatment approaches to further improve survival outcomes in pediatric ALL patients.

CONCLUSION

The outcomes of children with ALL during the induction phase of chemotherapy are influenced by several factors, including early diagnosis, risk stratification, and supportive care. However, in resource-limited settings such as Central India, nutritional status emerges as a critical determinant of outcomes. Malnourished children face a higher risk of treatment-related complications, prolonged neutropenia, and mortality.

Recommendations

1. Nutritional Support: Routine nutritional assessment and supplementation during ALL treatment may reduce complications and improve outcomes.
2. Supportive Care: Strengthening infection control measures and ensuring adequate supportive care during chemotherapy, including prophylactic antibiotics and growth factors, may reduce the incidence of febrile neutropenia and mortality.
3. Training and Infrastructure: Improving healthcare infrastructure, particularly in rural and resource-limited settings, and providing specialized training for healthcare professionals in pediatric oncology can enhance the management of ALL.
4. Research and Policy: Further research is needed to explore the role of nutritional interventions in improving outcomes for children with ALL, and policymakers should prioritize funding for childhood cancer care, particularly in low- and middle-income countries.

Through these efforts, the survival and quality of life of children with ALL in Central India and other resource-limited regions can be significantly improved.

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