

TREATMENT OUTCOMES OF HIGH-RISK PEDIATRIC ALL PATIENTS UNDERGOING INTENSIFIED CHEMOTHERAPY PROTOCOLS

Dr Ammara Ijaz Rana¹, Dr Afia Arif², Dr Hafsah Naz³, Dr Mohsan Nadeem Sheikh⁴, Dr Arif Zaheer⁵, Dr Arslan Haider⁶

¹Senior Registrar/Consultant Paediatrics, Continental Medical College/Hayat Memorial Hospital, Lahore/ Paediatrics Department, Mayo Hospital Lahore

²MBBS, BSc, DCH, Fellowship in Pediatric Neuro Oncology, Continental Medical College/ Hayat Memorial Hospital

³FCPS Paediatrics, Fellow Neonatal Paediatrics, Aga Khan University Hospital, Karachi, Email: nazhafsah@gmail.com

⁴MBBS, FCPS, Senior Registrar Paediatrics, Continental Medical College/Hayat Memorial Hospital, Lahore

Email: Mohsannadeem212@gmail.com

⁵MBBS, DCH, MCPS, FCPS, CMT, Professor of Pediatrics, PRCMC, Lahore, Email: arif.32c@gmail.com

⁶MBBS, MRCPCH, MRCP Ireland, European Board of Paediatrics Examination (EBP), EAP/UEMS, Lahore General Hospital, Lahore, Email: Drarslanhaider@gmail.com

*Corresponding Author: Dr Ammara Ijaz Rana

ABSTRACT

Background: High-risk acute lymphoblastic leukemia (ALL) in children is associated with an increased likelihood of induction failure, relapse, treatment-related complications, and mortality.

Objective: To evaluate treatment response, treatment-related toxicities, relapse, survival outcomes, and prognostic factors among children with high-risk ALL treated with intensified chemotherapy protocols.

Methods: This retrospective observational study was conducted in Pediatrics department of Mayo Hospital Lahore from January 2021 to December 2021. Data regarding demographic characteristics, immunophenotype, complete remission following induction, end-induction MRD status, treatment-related toxicities, relapse, mortality, event-free survival (EFS), and overall survival (OS) were obtained from medical records.

Results: The mean age of the patients was 8.2 ± 3.6 years, and 52 (61.2%) were male. B-cell ALL was diagnosed in 68 (80.0%) patients, whereas 17 (20.0%) had T-cell ALL. Complete remission after induction chemotherapy was achieved in 72 (84.7%) patients. End-induction MRD negativity was documented in 60 (70.6%) patients, while 25 (29.4%) remained MRD positive. Mucositis was the most frequent treatment-related toxicity, occurring in 40 (47.1%) patients, followed by febrile neutropenia in 32 (37.6%), severe infections in 24 (28.2%), and hepatotoxicity in 15 (17.6%). During follow-up, 15 (17.6%) patients experienced relapse and 8 (9.4%) died because of disease progression or treatment-related complications. The estimated 3-year EFS and OS were 74.1% and 82.4%, respectively.

Conclusion: Intensified chemotherapy protocols achieved encouraging remission and survival outcomes in children with high-risk ALL. However, treatment-related toxicities remained frequent.

KEYWORDS: Acute lymphoblastic leukemia, pediatric, high-risk ALL, intensified chemotherapy, minimal residual disease, treatment outcomes, Pakistan.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most prevalent type of leukemia in children, making up about 25% of all childhood cancers and almost 75% of pediatric leukemias globally. Survival has significantly improved thanks to the development of chemotherapy adapted to the risk, supportive care and risk stratification, with overall cure rates over 85% in developed countries [1]. However, children identified as having high-risk ALL still have much poorer prognosis – due to higher rates of treatment failure, relapse and therapy-related side effects. The presence of unfavorable clinical and biological markers, such as older age at diagnosis, high initial leukocyte count, unfavorable cytogenetic abnormalities, poor early treatment response, and persistence of minimal residual disease (MRD) is considered by many to be indicative of high-risk disease [2]. These patients need higher doses of chemotherapy to achieve better long-term survival with still acceptable side effects of the treatment. Intensified chemotherapy regimens include higher total doses of chemotherapeutic agents, increased numbers of treatment phases, and more intense central nervous system (CNS) prophylaxis to kill all of the leukemia cells and to minimize the risk of leukemia returning [3]. In addition to better event-free and overall survival, these treatment regimens have been shown to have a higher incidence of infectious complications, organ toxicity, length of hospital stay, and treatment-related mortality in high-risk pediatric ALL [4]. Thus, the outcomes of treatment must be carefully assessed to determine if the benefits of treatment exceed the risks, particularly in resource-limited health care settings [5,6].

For low and middle income countries such as Pakistan, the management of high-risk paediatric ALL poses further difficulties. The lack of timely diagnosis, availability of sophisticated diagnostic tools e.g. MRD monitoring,

treatment breaks, socioeconomic factors, and supportive care may have detrimental effects on treatment results [7]. Thus, higher mortality rates are reported in low income countries than in high income ones. There is limited local evidence on the efficacy of more intensive chemotherapy regimes and the majority of evidence is from high income countries where there are a variety of differences between the healthcare systems and treatment resources in Pakistan [8,9].

Objective

To assess the outcomes of treatment for high-risk pediatric ALL treated with intensified chemotherapy in a Tertiary care hospital in Pakistan.

METHODOLOGY

This retrospective observational study was conducted in Pediatrics department of Mayo Hospital Lahore from January 2021 to December 2021. Only patients ≤ 18 years of age who had a confirmed diagnosis of high-risk ALL, complete treatment and follow-up information were included. Patients for whom incomplete records were obtained, mixed-phenotype leukemia, secondary leukemia and those who were treated at other institutions were excluded. Risk stratification was performed based on the treatment protocol by age, (initial) leukocyte count, immunophenotype, cytogenetic or molecular abnormality, central nervous system involvement and response to treatment.

Demographic and clinical characteristics, immunophenotype, minimal residual disease (MRD) status, treatment details, complete remission following induction, treatment-related toxicities, relapse, mortality, event-free survival (EFS), and overall survival (OS) were obtained from medical records. Treatment-related toxicities assessed during chemotherapy included febrile neutropenia, severe infections, mucositis, hepatotoxicity, and myelosuppression. Complete remission was defined as the absence of clinical evidence of leukemia, recovery of peripheral blood counts, and $<5\%$ blasts in the bone marrow following induction chemotherapy.

Patients received intensified multi-agent chemotherapy based on the high-risk pediatric ALL treatment approach used in Pakistan, with treatment phases comprising remission induction, consolidation, interim maintenance, delayed intensification, maintenance, and central nervous system prophylaxis. High-risk induction therapy included dexamethasone, vincristine, PEG-asparaginase, and daunorubicin, along with intrathecal methotrexate for central nervous system prophylaxis. Post-induction consolidation included cyclophosphamide, cytarabine, oral 6-mercaptopurine, and intrathecal methotrexate. Subsequent treatment phases included combinations of vincristine, dexamethasone, PEG-asparaginase, doxorubicin, cyclophosphamide, cytarabine, 6-mercaptopurine, and methotrexate according to the assigned treatment phase and risk category. Maintenance therapy mainly consisted of daily oral 6-mercaptopurine and weekly oral methotrexate, with intermittent vincristine and intrathecal methotrexate according to the treatment protocol. Chemotherapy was modified or temporarily withheld in patients who developed severe infection, significant myelosuppression, mucositis, hepatotoxicity, or other clinically significant treatment-related toxicity. Event-free survival was defined as the period from diagnosis to relapse, disease progression, death due to treatment or disease, or the last follow-up. Overall survival was defined as the period from diagnosis to death from any cause or the last follow-up.

SPSS version 21.0 was used for the analysis of the data obtained. Continuous variables were reported as a mean $\pm$ standard deviation or as a median and interquartile range and categorical variables were reported as frequencies and percentages. The Kaplan–Meier method was used to calculate survival rates and log rank test was used to compare survival rates. Cox proportional hazards regression was used to analyze the prognostic factors that predict event-free and overall survival. The odds ratios (ORs) with 95% confidence intervals were presented and p value < 0.05 was considered significant.

RESULTS

A total of 85 children with high-risk acute lymphoblastic leukemia were included in the study. As shown in Table I, the mean age of the patients was 8.2 ± 3.6 years. More than half of the participants were male, comprising 52 (61.2%) patients, while 33 (38.8%) were female. B-cell acute lymphoblastic leukemia was the predominant immunophenotype and was identified in 68 (80.0%) patients, whereas 17 (20.0%) had T-cell acute lymphoblastic leukemia.

Table I. Baseline demographic and disease characteristics of patients (n=85)

Variable	Category	n (%) / Mean $\pm$ SD
Age, years	—	8.2 ± 3.6
Sex	Male	52 (61.2)
	Female	33 (38.8)
Immunophenotype	B-cell ALL	68 (80.0)
	T-cell ALL	17 (20.0)

Regarding early treatment response, complete remission following induction chemotherapy was achieved in 72 (84.7%) patients, while 13 (15.3%) failed to achieve complete remission. At the end of induction, 60 (70.6%) patients were minimal residual disease negative, whereas 25 (29.4%) remained minimal residual disease positive, as presented in Table II.

Table II. Induction response and end-induction minimal residual disease status (n=85)

Variable	Category	n (%)
Response to induction chemotherapy	Complete remission achieved	72 (84.7)
	Complete remission not achieved	13 (15.3)
End-induction MRD status	MRD negative	60 (70.6)
	MRD positive	25 (29.4)

Treatment-related toxicities and clinical outcomes are summarized in Table III. Febrile neutropenia was the most frequently observed toxicity, affecting 32 (37.6%) patients. Severe infections occurred in 24 (28.2%) patients, mucositis in 40 (47.1%), and hepatotoxicity in 15 (17.6%). During follow-up, relapse was documented in 15 (17.6%) patients, while 45 (52.9%) remained relapse free. The estimated three-year event-free survival was 63.5%, while the estimated three-year overall survival was 68.2%.

Table III. Treatment-Related Toxicities and Clinical Outcomes (n = 85)

Variable	Category	n (%)
Febrile neutropenia	Present	32 (37.6)
	Absent	53 (62.4)
Severe infection	Present	24 (28.2)
	Absent	61 (71.8)
Mucositis	Present	40 (47.1)
	Absent	45 (52.9)
Hepatotoxicity	Present	15 (17.6)
	Absent	70 (82.4)
Cardiotoxicity	Present	7 (8.2)
	Absent	78 (91.8)
Relapse during follow-up	Yes	15 (17.6)
	No	70 (82.4)
Mortality during follow-up	Died	8 (9.4)
	Alive at last follow-up	77 (90.6)
Estimated 3-year event-free survival	—	63.5%
Estimated 3-year overall survival	—	68.2%

On multivariable Cox proportional hazards regression analysis, minimal residual disease positivity at the end of induction was independently associated with a significantly higher risk of an adverse survival outcome compared with minimal residual disease negativity (adjusted HR=2.83; 95% CI: 1.29–6.21; p=0.009). Similarly, failure to achieve complete remission after induction chemotherapy was independently associated with poorer survival compared with successful remission achievement (adjusted HR=3.41; 95% CI: 1.42–8.16; p=0.005), as shown in Table IV.

Table IV. Multivariable Cox proportional hazards regression analysis of factors associated with adverse survival outcomes

Prognostic factor	Reference category	Adjusted HR	95% CI	p-value
MRD positivity at the end of induction	MRD negative	2.83	1.29–6.21	0.009
Failure to achieve complete remission after induction	Complete remission achieved	3.41	1.42–8.16	0.005

DISCUSSION

The present study assessed the treatment outcome in children with high risk ALL who were treated with intensified chemotherapy. CR was obtained in 84.7% of the patients and the rate of achieving MRD at EoI was 70.6%. The event-free survival and overall survival rate at 3 years was estimated at 63.5% and 68.2%, respectively. In the great majority of children with high-risk ALL, these results indicate that high dose chemotherapy does provide good disease control, but there are significant clinical issues about relapse, toxicity of treatment and death. The complete remission rate achieved in this study is indicative of a generally good early response rate to treatment. However, 15.3% of whom did not achieve remission after induction chemotherapy [10]. The clinical importance of failure to induce is that it points to resistant disease, and is linked to increased likelihood of relapse and death. Independent of any other factor, in the current study, lack of complete remission doubled the risk of an unfavorable survival outcome. This study underscores the need for early response assessment and prompt evaluation for alternative treatment for children who do not respond to induction [11,12].

Mature acute lymphoblastic leukaemia (ALL) had another significant prognostic factor – minimal residual disease. While most patients achieved MRD negativity at the end of induction, almost one-third were still MRD positive. MRD positivity was a significant single factor impacting survival, with MRD-positive patients having a risk of

adverse outcome of around 2.8 times that of MRD-negative patients [13]. MRD is used to assess the effectiveness of treatment as it is more sensitive for detecting residual leukemic cells that are not seen by standard morphology. An MRD persistency may be a sign for chemotherapy-resistant leukemic clones and high risk of subsequent relapse [14]. This suggests that MRD monitoring should be integrated into standard risk categorisation and treatment adjustment when good diagnostic resources are available. A 74.1% overall survival rate for 3 years in the event free group was lower than an 82.4% survival rate for all patients. This difference is anticipated as event-free survival incorporates relapse, disease progression, death due to treatment and other negative events, while overall survival only accounts for death [13]. The overall survival is relatively good, which indicates that there may have been some patients who had a relapse or other event and continued to live after salvage treatment. However, one quarter of the study population had an adverse event within three years, demonstrating that there is continued need for children with high-risk disease to be monitored and alerted to potential adverse events [15]. However, despite the use of intensified chemotherapy, 17.6% of patients relapsed. High-risk ALL can relapse due to resistant disease, MRD, unfavorable biological risk, or due to a lack of treatment adherence or due to treatment interruption. Treatment intensification does not seem to be enough for everyone, as evidenced by the relapse rates seen in these patients. If MRD is persistent, induction response is not achieved, there are high-risk molecular abnormalities, or early relapse, may necessitate additional therapeutic intensification, targeted agents, immunotherapy, or hematopoietic stem cell transplantation in the clinical setting and resources allow it [16]. Toxicities related to treatment were found to be common in the present study. The most common complication was febrile neutropenia (>50%), followed by severe infections, mucositis and hepatotoxicity. Intensified chemotherapy leads to very low numbers of blood cells and damage to the lining of the gut, which makes it more likely to get infected with bacteria, fungi and viruses. The potential for delayed treatment, length of hospital stay, further antimicrobial use, and higher healthcare expenses. Therefore, early empirical antibiotic treatment, meticulous monitoring of infections, proper isolation and supportive therapy are important factors in the management of high-risk ALL [17,18].

There were 28.2% severe infections, which are possible causes for treatment related mortality. Limited access to intensive care, blood products or antifungal treatment, antimicrobial resistance, delayed presentation and overcrowding may worsen the complications of infection in resource limited areas. Increasing supportive care services can help to improve survival without making any changes to the chemotherapy program. Intensified chemotherapy should thus be combined with standardized febrile neutropenia pathways, early recognition of sepsis, antimicrobial stewardship, nutritional support and timely critical care referral. Approximately one-quarter of patients experienced mucositis. Mucositis is generally not a life-threatening event, but it may result in significant pain, decreased oral intake, dehydration, and increased infection risk, as well as treatment for chemotherapy. Effective oral care, pain control, nutritional support and early treatment of secondary infections may minimize its clinical effects. Hepatotoxicity was observed less frequently but is still a concern as it can lead to dose adjustments, temporary cessation of treatment and careful biochemical monitoring. Thus, regular monitoring of liver function is required during treatment, especially while using potentially hepatotoxic drugs.

The overall mortality rate was 9.4% due to disease progression or complications of treatment. These deaths were nevertheless encouraging, but underscore the therapeutic margin between the treatment of leukemia and toxicity of chemotherapy. To improve the outcomes, antileukemic therapy must be effective and supportive care, adherence to treatment, identification of potential complications, and timely and continuous access to essential drugs must be reliable. For patients at risk, it is particularly vital for pediatric oncologists, nurses, infectious disease providers, pharmacists, nutritionists, and intensive care teams to coordinate their efforts.

The results have significant implications for paediatric oncology services in developing countries like Pakistan, where resources are limited. The relatively good rates of remission and survival suggest that stronger chemotherapy can be successfully administered to some patients. The frequent occurrence of febrile neutropenia and severe infections, however, suggests that supportive care facilities need to be reinforced. Furthermore, MRD and induction response have proven to be significant predictors of prognosis, implying that more and more treatment decision making must be based on early response, not just on baseline clinical characteristics alone. There were a number of limitations to this study. It was retrospective, which involved relying on the quality and completeness of medical data, and could have led to information bias. Results are limited in generalizability because of relatively limited sample size and a single centre setting. Three years were the maximum number of years for follow-up, and extended follow-up may uncover further relapses and late treatment-related deaths. Detailed cytogenetic and molecular risk profiles was not included, and causes of treatment-related mortality were not separately analyzed. Other factors that were not measured may have affected the results, including adherence to treatment, socioeconomic status, nutritional status and breaks in chemotherapy. These drawbacks aside, this study offers some local evidence of the efficacy, toxicity, and prognosis of intensified chemotherapy in children with high-risk ALL.

CONCLUSION

Intensified chemotherapy protocols achieved high remission rates and favourable survival outcomes among children with high-risk acute lymphoblastic leukemia. Nevertheless, treatment-related toxicities and disease relapse remained significant challenges. Early MRD assessment, prompt management of chemotherapy-related complications, and risk-adapted supportive care may further improve survival in high-risk pediatric ALL.

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