IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Minimal Residual Disease in Acute Lymphoblastic Leukaemia and Its Relationship with Other Prognostic Factors

Chinmayee Agrawal[1], Sai Madhuri Boppana[2], Santhosh K Devdas[1], Vinayak V Maka[1], Nalini Kilara[1], Swaratika Majumdar[1], Rasmi Palassery[1]

[1]Department of Medical Oncology, Ramaiah Medical College, Bengaluru, India
[2]Department of Medical Oncology, NRI Medical College and Hospital, Mangalagiri, Andhra Pradesh, India

Corresponding Author: Rasmi Palassery, Department of Medical Oncology, Ramaiah Medical College, Bengaluru, India
E-mail: rasmipalassery@gmail.com

Received: 10, Oct, 2023
Accepted: 27, Feb, 2024

ABSTRACT

Background: Minimal Residual Disease (MRD) assessment is crucial for directing treatment decisions in Acute Lymphoblastic Leukemia (ALL). In low- and middle-income countries, limited resources can present challenges to implementing MRD-guided therapy intensification for ALL. The study attempted to assess the relationship between MRD and other prognostic factors in ALL, focusing on treatment outcomes and disease progression.

Materials and Methods: A retrospective observational study was conducted at Ramaiah Medical College and Hospital in Bengaluru, examining patient data from January 2021 to December 2021. MRD status was determined post-induction using flow cytometry. Patients were classified into various groups based on factors such as type of ALL (B-cell or T-cell), NCI risk status (standard or high), cytogenetic risk (favorable, poor, or intermediate), CNS status, prednisone response, and MRD levels at the end of induction.

Results: Out of 72 patients, 25% were MRD-positive, with a male: female ratio of 2.13:1. B-ALL was diagnosed in 49 patients and T-ALL in 23, with 75% categorized as high-risk by NCI criteria. Cytogenetic analysis revealed a diverse profile (23.61% PR, 48.61% IR, 27.78% FR), and 58.33% exhibited a good prednisone response (GPR). At the end of the induction phase, 25% tested positive for MRD, with B-ALL showing a lower MRD rate at 15.2%. Age and NCI risk status significantly influenced MRD outcomes, with 75% of participants classified as high-risk.

Conclusion: This study demonstrates a significant association between MRD positivity and factors such as age, NCI risk status, and B-ALL diagnosis, underscoring the complex interaction of these variables in predicting treatment outcomes for ALL patients.

Keywords: Leukemia; Lymphoid; Minimal residual disease; Flow cytometry; Healthcare disparities; Prognosis

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) originates from lymphoid precursor cells and remains a significant clinical challenge due to its diverse presentations and treatment outcomes[1]. Encouragingly, advancements in diagnostic and therapeutic techniques have led to improved prognosis for patients. Pulte et al. in 2020 found that the 5-year survival rate for ALL patients has increased to 75%. Among these advancements, the role of Minimal Residual Disease (MRD) assessment has been pivotal[2].

MRD refers to the residual leukemic cells undetectable by traditional microscopic methods. Advanced techniques, such as PCR amplification of specific fusion genes and flow cytometry, have made detecting these cells post-treatment possible[3]. The study conducted by Heuser et al. in 2021 underscored the significance of MRD detection, demonstrating that patients with undetected MRD

DOI: 10.18502/ijhoscr.v19i1.17822

had a 15% lower risk compared to those in whom MRD was detected. This information is crucial for clinicians to assess treatment efficacy, anticipate disease progression, and make informed patient care decisions[4].

The progression of ALL is influenced by a range of prognostic factors, including age, immunophenotype, cytogenetic abnormalities, early treatment response, and risk stratification. Collectively, these factors determine the disease's trajectory. The dynamic relationship between MRD and these factors is crucial for understanding disease progression and outcomes[5]. Research conducted by Kayser et al. in 2019 indicated that patients with certain cytogenetic abnormalities who also tested positive for MRD had a relapse rate nearly twice as high as those without these abnormalities[6].

However, there is a disparity in the availability of MRD detection across different regions. In areas with limited resources, the absence of MRD detection can lead to compromised treatment outcomes. Munshi et al. in 2020 found that regions without access to MRD detection had a 20% lower survival rate in ALL patients than those with comprehensive healthcare infrastructure[7]. Given these findings, the present study intends to further explore the relationship between MRD and established prognostic factors in ALL. By elucidating how MRD interacts with determinants like age, immunophenotype, and early treatment response, the study aims to refine the predictive framework for ALL outcomes, especially in under-resourced settings.

MATERIALS AND METHODS

The current study is a retrospective observational investigation conducted at Ramaiah Medical College and Hospital in Bengaluru. It reviewed patient data from January 2021 to December 2021, which included records from September 2015 to December 2021. Data were extracted from the haematology unit, both from digital case records and physical files stored in the medical record section. Ethical approval was obtained from the Institutional Review Board of Ramaiah Teaching and Memorial Hospital (registration number: DRP/IFP828/2022, issued on 03/02/2022), ensuring the study's compliance with the Declaration of Helsinki, and informed consent was obtained from study participants.

Based on incidence rates from previous studies on ALL, the required sample size was calculated at 72 patients, accounting for a 95% confidence level and an 11% absolute precision[8]. The included patients were diagnosed with ALL and had undergone immunophenotyping, cytogenetic studies, and CSF analysis at diagnosis. Additionally, these patients completed BFM-based induction chemotherapy and had bone marrow analysis at the end of induction. Three patients given mini-hyper CVAD due to advanced age were also included. Patients excluded were those who did not receive induction chemotherapy at the center. The status of MRD was determined at the end of induction using flow cytometry. MRD was conducted using 12-color flow cytometry on a FACS lyric machine.

Patients were then classified based on the following criteria: (i) ALL subtype (B or T cell ALL); (ii) NCI risk group (standard or high risk); (iii) cytogenetic risk (favorable risk like t(12;21) or hyperdiploidy, poor risk factors like hypodiploidy, t(9;22), MLL translocation, t(1;19), iAMP21, IKZF1 deletion, and intermediate risk which is neither favorable nor poor); (iv) CNS involvement (positive or negative); (v) prednisone response (good or poor); (vi) MRD status at the end of induction (either less than 0.01% or more than 0.01%).

The data were collected using Microsoft Excel. Baseline characteristics, demographic details, and treatment information were recorded. This included variables such as age, gender, ALL subtype, NCI risk group, cytogenetic risk, CNS involvement, prednisone response, and MRD status at the end of induction. The data cleaning was done before statistical analysis to ensure accuracy and completeness.

For statistical analysis, SPSS version 21 was used. Chi-square tests compared the "Achieved Remission" group with the "No Remission" group, focusing on variables such as age, ALL subtype, NCI risk group, cytogenetics, and prednisone response. A p-value of less than 0.05 was considered statistically significant. frequencies, and for continuous variables, described as means with standard deviations or medians with

ranges. The relationship between post-induction chemotherapy results and patient categories was also assessed.

RESULT

In this study, the effects of induction chemotherapy on the disease status in patients with B and T cell ALL were evaluated, focusing on bone marrow morphology and MRD results. The analysis included a cohort of 72 patients with a median age of 13 years. Specifically, 40.28% (29 patients) were 10 years old or younger, and 59.72% (43 patients) were older than 10 years. The gender distribution was skewed toward males, as indicated by a male-to-female ratio of 2.13:1, suggesting a higher prevalence of the disease in male patients (Table 1).
In the immunological subtypes of ALL, 49 patients (68.05%) were identified with B-ALL, while 23 patients (31.95%) had T-ALL. Per NCI criteria, 54 patients (75%) were marked as high-risk. In cytogenetic analysis, 17 patients (23.61%) fell into the poor risk category, 35 patients (48.61%) were assigned to the intermediate risk group, and 20 patients (27.78%) emerged as good risk (Table 1). Additionally, 54 patients (75%) showed a positive response to prednisone.
Out of the group, 18 patients (25%) had positive MRD. The analysis revealed that B-ALL patients had a lower MRD positivity rate of 15.27%. Patients with NCI standard risk showed even lower MRD positivity at 1.38% (p=0.03*), those with favorable cytogenetics at 5.55%, and those with a good response to prednisone at 13.88%. Age (p=0.03*) and NCI risk status were significant factors affecting MRD positivity, with odds ratios of 0.34 and 0.10, respectively (Table 2). The subtype (B cell vs. T cell) and cytogenetics did not show statistically significant differences in MRD positivity (p=0.45 and p=0.77, respectively). Prednisone response approached statistical significance (p=0.06), suggesting a potential trend.

Table 1: Patient Characteristics

Parameters	Values
Total Patients (N)	72
Age (Median, years)	13 (Range: 1-58 years)
Gender	
Male	49 (68.5%)
Female	23 (31.95%)
Subtype	
B-ALL	49 (68.5%)
T-ALL	23 (31.95%)
NCI Risk	
Standard Risk (SR)	18 (25%)
High Risk (HR)	54 (75%)
Cytogenetics	
Poor Risk (PR)	17 (23.61%)
Intermediate Risk (IR)	35 (48.61%)
Good Risk (GR)	20 (27.78%)
Day 8 Peripheral Blood Blast	
Present	18 (25%)
Absent	54 (75%)

Table 2: Parameters Affecting MRD Outcomes

Parameters	Categories	MRD Positive (n)	MRD Negative (n)	Not Available (n)	Chi-square (P)
Age	≤10 years	5	22	2	0.03862*
	>10 years	13	20	10	
Subtype	B Cell	11	31	7	0.458256
	T Cell	7	11	5	
NCI-Risk Group	Standard Risk	1	15	2	0.036054*
	High Risk	17	27	10	
Cytogenetics	Poor Risk	5	9	3	0.778758
	Intermediate Risk	9	19	7	
	Good Risk	4	14	2	
Prednisone Response	Good Response	10	32	12	0.062402
	Poor Response	8	10	-	

P <0.05*

DISCUSSION

Many studies have underscored the clinical importance of MRD in ALL[9,10,11]. Campana et al. found that MRD status following induction therapy is a key predictor of outcomes, especially in children and adolescents with ALL[12]. Similarly, Gajjar et al. observed a significant association between MRD positivity and treatment outcomes[13]. These consistent findings emphasize the critical role of achieving MRD negativity after the initial treatment phase, as it is often linked to better long-term prognoses for patients.

MRD-guided therapy has become a fundamental approach in ALL management. The detection of MRD at different stages of treatment, such as during induction and consolidation, enables clinicians to tailor treatment strategies accordingly. Patients with persistent MRD positivity might require more intensive treatments, like stem cell transplantation, to improve treatment effectiveness. On the other hand, those who clear MRD quickly might benefit from reduced treatment to minimize long-term side effects. This approach is especially relevant in light of Malard et al.'s findings that ALL is more prevalent in young children, typically between ages 1 and 4[14]. The current study presents similar trends, with 40.28% of patients being 10 years or younger and an average age of 13. Additionally, the study observed a slightly higher prevalence in male patients, with a ratio of 2.13:1.

In the present study, the MRD positivity rate was 25% at the end of the induction phase, indicating a significant remaining disease burden. This rate is higher than the 20% reported by Borowitz et al., suggesting a potentially higher risk in the patient study group[9]. Age and NCI risk status significantly influenced MRD positivity, with patients aged 10 years or younger and those classified under standard NCI risk showing a lower likelihood of MRD. These findings are in line with Vora et al., who noted improved outcomes in younger patients, underscoring the importance of considering age and NCI risk status in treatment planning[15].

The findings of the present study regarding the distribution of B-cell precursor ALL (B-ALL) and T-cell ALL (T-ALL) align with established trends and mirror the results reported by Dunwell et al. The findings of the current study state that B-ALL accounted for approximately 68.5% of cases, while T-ALL made up 31.95%. This distribution reflects the generally higher prevalence of B-ALL compared to T-ALL. Distinguishing between these subtypes is crucial, as they possess different genetic and clinical features that significantly influence treatment approaches and patient outcomes. This concurs with the emphasis in Dunwell et al.'s study on the importance of identifying these subtypes for the development of appropriate therapeutic strategies[16].

The findings of the current study show that 75% of patients meet the NCI high-risk criteria, highlighting the aggressive nature of the disease and the need for personalized treatment based on individual genetic profiles. Furthermore, 48.61% of patients fall into the intermediate-risk category, while 27.78% are classified as good risk in terms of cytogenetics, emphasizing the variety of cytogenetic abnormalities

in ALL and the necessity for tailored treatment strategies. In contrast, a study by Winick et al. reported that 64.1% of cases were classified as standard risk, with 35.9% in the high-risk category[17]. When examining outcomes by NCI risk group, patients with NCI-categorized standard-risk or high-risk CNS1 disease demonstrated significantly better outcomes. Notably, a subset of patients with NCI-categorized standard-risk disease, characterized by favorable blast cell genetics and a positive response to initial treatment, showed favorable outcomes. These findings reinforce the importance of risk-based treatment approaches in the management of ALL.

MRD assessment has revolutionized the management of ALL by offering precise measures of treatment response and associated risks. Integrating MRD monitoring into treatment plans potentially optimizes therapeutic approaches and enhances patient outcomes. With technological advances and better standardization, MRD detection is becoming a crucial part of ALL treatment protocols, significantly contributing to more effective disease control and improved patient survival[18]. However, it's important to note the limitations of our study, especially the lack of sufficient baseline data on cytogenetics and MRD testing at the end of induction for some patients, mainly due to logistical constraints.

CONCLUSION

MRD assessment at the end of induction was identified as a crucial factor in guiding treatment decisions. This study observed a distribution of ALL subtypes consistent with established patterns, with B-ALL (68.5%) being more common than T-ALL (31.95%). A significant majority of patients (75%) were classified under the NCI high-risk criteria, underscoring the necessity for personalized treatment based on genetic profiles. Additionally, younger age, with patients aged 10 years or younger, and those classified under standard NCI risk correlated with a lower likelihood of MRD positivity. The study recognizes the challenges in the widespread adoption of MRD but emphasizes its potential in optimizing treatment strategies and improving patient outcomes

REFERENCES

1. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350(15):1535-48.
2. Pulte D, Gondos A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. Blood. 2009;113(7):1408-11.
3. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). Blood. 2009;113(18):4153-62.
4. Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021;138(26):2753-67.
5. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115(16):3206-14.
6. Kayser S, Levis MJ. Clinical implications of molecular markers in acute myeloid leukemia. Eur J Haematol. 2019;102(1):20-35.
7. Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv. 2020;4(23):5988-5999.
8. Tembhare PR, Sriram H, Khanka T, et al. Flow cytometric evaluation of CD38 expression levels in the newly diagnosed T-cell acute lymphoblastic leukemia and the effect of chemotherapy on its expression in measurable residual disease, refractory disease and relapsed disease: an implication for anti-CD38 immunotherapy. J Immunother Cancer. 2020;8(1): :e000630 .
9. van Dongen JJ, Seriu T, Panzer-Grümayer ER, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet. 1998;352(9142):1731-8.
10. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111(12):5477-85.
11. Jeha S, Choi J, Roberts KG, et al. Clinical significance of novel subtypes of acute lymphoblastic leukemia in the context of minimal residual disease–directed therapy. Blood Cancer Discov. 2021;2(4):326-337.
12. Coustan-Smith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. Blood. 2000;96(8):2691-6.

13. Coustan-Smith E, Gajjar A, Hijiya N, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia after first relapse. Leukemia. 2004;18(10):1727-8.
14. Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet. 2020;395(10230):1146-62.
15. Stutterheim J, van der Sluis IM, de Lorenzo P, et al. Clinical implications of minimal residual disease detection in infants with KMT2A-rearranged acute lymphoblastic leukemia treated on the interfant-06 protocol. J Clin Oncol. 2021;39(6):652-662.
16. Dunwell TL, Hesson LB, Pavlova TV, et al. Epigenetic analysis of childhood acute lymphoblastic leukemia. Epigenetics. 2009;4(3):185-93.
17. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012;30(14):1663-9.
18. Pui CH, Jeha S. New therapeutic strategies for the treatment of acute lymphoblastic leukaemia. Nat Rev Drug Discov. 2007;6(2):149-65 .