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Clinical Profile, Toxicities, and Survival Outcome of MCP841 in Pediatric Acute Lymphoblastic Leukemia in Current Era: A Retrospective Study from Eastern India

Swarnabindu Banerjee[1] Sanjukta Saha[2] Dibyendu Raychaudhuri[2] Mihir Sarkar[2] Kalpana Datta[2]

[1] Department of Medical Oncology, Medical College and Hospital, Kolkata, India
[2] Department of Paediatrics, Medical College and hospital, Kolkata, India

Address for correspondence Dr. Sanjukta Saha, MD (Paediatrics), 2 Dasnagar Road, Birati, Kolkata 700051, India (e-mail: saha1294@gmail.com).

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Abstract

Introduction: The overall survival in pediatric acute lymphoblastic leukemia (ALL) ranges from 45 to 81% in India. Aggressive chemotherapy protocols like MCP841 have improved the outcome and it can be delivered with minimal supportive care. This study retrospectively analyses the clinical profile and overall survival of patients treated by this protocol.

Objective: This single-center study aims to estimate the event-free survival of patients treated accordingly to the MCP841 protocol with high-dose cytarabine (HDAC) at 2 g/m^2 as the backbone, along with the risk-stratified incidence and cause of mortality in childhood ALL.

Material and Methods: Records of 156 patients aged 1 to 19 years, newly diagnosed with ALL from June 2009 to August 2013 who were treated according to the forementioned protocol were analyzed. Risk stratification for both precursor B-cell ALL (B-ALL) and T-cell ALL (T-ALL) was done, followed by an analysis of the correlation of risk-stratified groups with mortality and survival outcomes.

Result: Precursor B-ALL was found in 70% patients (including 69.7% [$n = 76$] standard risk, 20.1% [$n = 22$] intermediate risk, and 10% [$n = 11$] high risk), while 30% had T-ALL (including 74.4% [$n = 35$] standard risk and 25.5% [$n = 12$] high risk). Death during induction occurred in 0.04% ($n = 5$) precursor B-ALL and 23% ($n = 11$) T-ALL patients. The causes were infection in 62.5%, hemorrhage in 25%, and cortical venous thrombosis in 12.5%. Among those who attained remission (89.7%, $n = 140$), relapse occurred in 26% ($n = 27$) precursor B-ALL and 28% ($n = 10$) T-ALL patients. Approximately 31% patients died in the postinduction phase, with progressive disease due to relapse being the most common cause and bone marrow the most common site. Event-free survival at 168 months for overall population, precursor B-ALL, and T-ALL was 59, 62.4, and 51.1%, respectively.

Conclusion: A comparable survival outcome in par with similar centers in developing countries with the MCP841 protocol was found. Infections are a major cause of

Keywords
- acute lymphoblastic leukemia
- high-dose cytarabine
- MCP841 protocol
- retrospective study
- survival analysis

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mortality during treatment, especially when associated with malnourishment. Relapsed disease and poor salvage rates remain a major hurdle to achieving better survival in developing countries; however, better supportive care and infection control measures along with implementing risk-stratified high-dose chemotherapy protocols might improve outcome in the future.

Introduction

Acute lymphoblastic leukemia (ALL) is one of the most common malignancies in children in India with relative proportion varying between 25 and 40%.[1] After the introduction of aggressive chemotherapy protocols like Berlin–Frankfurt–Münster (BFM), remarkable outcome has been seen in the developed countries resulting in cure rate of 80 to 90%.[2] The prognosis of ALL in India remains poor as the overall survival in ALL ranges from 45 to 81%.[3–7] This can be partly attributed to the logistic constraints to tackle side effects of aggressive protocols and nonadherence to treatment. Aggressive chemotherapy protocols, therapy stratification, and risk-adapted management represent major cornerstones in the treatment of childhood ALL.[8,9] The MCP841 protocol was developed for low- and middle-income countries as it can be delivered with minimal supportive care.[10]

Initially high-dose cytarabine (HDAC) at the dose of 2 g/m^2 were given to those younger than 3 years who could not be given prophylactic cranial radiation. At the Tata Memorial Hospital, Mumbai, HDAC at the dose of 2 g/m^2 was given to entire pediatric population, and the 4-year event-free survival (EFS) was reported to be 85.5%, which is at par with the EFS reported in cancer centers in developed countries. The incidence of posttherapy relapse was reported to be 15% in the MCP841 protocol in a study at the same center.[8]

Our primary objective was to study the EFS with HDAC as the backbone of the protocol.

The secondary objectives of the study were to determine the following:

- Incidence of precursor B-cell ALL (B-ALL; standard, intermediate, and high risk) and T-cell ALL (T-ALL; standard and high risk) as per the criteria listed in ►**Table 1**.

Table 1 Criteria for risk stratification

B-cell precursor ALL	Standard risk (precursor B-ALL SR)	• Children aged >1 and <10 y • WBC count <50,000/mm^3 at presentation • Prednisolone good responder • No testicular or bulky disease • No high-risk cytogenetics
	Intermediate risk (precursor B-ALL IR)	• Children ≥10 y or WBC count ≥50,000/mm^3 at presentation OR • Testicular or bulky disease AND • Prednisolone good responder • No high-risk cytogenetics
	High risk (precursor B-ALL HR)	• High-risk cytogenetics t(9:22), translocations of chr.11, complex cytogenetics • OR prednisolone poor responder • OR central nervous system disease
T-cell ALL	Standard risk (T-ALL SR)	• WBC count <10,000/mm^3 at presentation • No bulky disease • Prednisolone good responder • Complete remission at the end of induction • Not ETP-ALL • No CNS disease
	High-risk (T-ALL HR)	Any of the following: • WBC ≥100,000/mm^3 at presentation • Bulky disease • ETP phenotype • T lymphoblastic lymphoma • Prednisolone poor responder • No complete remission after induction • CNS disease

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; ETP, early T-cell precursor ALL; HR, high risk; IR, intermediate risk; SR, standard risk; WBC, white blood cell.

- Incidence and cause of death in various risk groups of ALL.
- Statistical correlation of risk stratification with mortality.

Materials and Methods

In this retrospective observational study, data of 156 patients aged 1 to 19 years diagnosed with ALL from June 2009 to August 2013 at the Medical College and Hospital, Department of Medical Oncology and Department of Pediatrics, were analyzed. Immunophenotyping and conventional cytogenetic study were planned in all cases at diagnosis, but this was subject to logistic issues and nonavailability. The patients were treated according to the MCP841 protocol with HDAC (2 g/m^2 every 12 hours for 2 days, repeated every 14 days for 3 cycles) for the entire population. The chemotherapy protocol followed is depicted in ►**Table 2**. Prophylactic cranial irradiation was given to children older than 3 years. Individuals were stratified into various risk groups as per the criteria mentioned in ►**Table 1**. Complete blood count (CBC) was performed thrice weekly and cerebrospinal fluid (CSF) examination was performed as per protocol to detect the central nervous system (CNS) relapse. Prednisone response was defined as reduction in a number of blood blasts per microliter after a 7-day prednisone prephase and one intrathecal dose of methotrexate on day 1. Prednisolone good response (PGR) is less than 1,000 blasts/µL, whereas prednisolone poor response (PPR) is ≥1,000 blasts/µL.[9] Remission death has been defined as death after remission and before completion of maintenance. Fluorescence in situ hybridization (FISH) cytogenetics and molecular genetics were avoided for risk stratification as they were not available during the study period across the population.

Supportive management and neutropenic care were instituted for all patients as per the institutional protocol. Investigations such as CBC, C-reactive protein, and blood culture were done in all suspected cases of sepsis and febrile neutropenia. Initial empirical antibiotics used were piperacillin-tazobactam and amikacin. Antibiotics were changed according to culture sensitivity reports. When neutropenic sepsis was associated with no identified organisms in blood culture, the choice of antibiotics was piperacillin-tazobactam + amikacin (first line), followed by meropenem + vancomycin (second line), and, finally, colistin and antifungals. Antifungals used for treatment were amphotericin B and voriconazole.

Primary outcome: To study the EFS with HDAC as the backbone of the protocol.

Secondary outcome: To estimate the incidence of risk-stratified ALL in pediatric patients and to determine the incidence and cause of death in various risk groups.

Inclusion Criteria

Patients aged 1 to 19 years newly diagnosed with ALL from June 2009 to August 2013 and treated according to the MCP841 protocol with HDAC (2 g/m^2) were included in the study.

Exclusion Criteria

Treatment defaulters during any phase of treatment till re-intensification (RI_1) and previously treated cases of ALL were excluded from the study.

Table 2 Summarizing MCP841 chemotherapy protocol

Drugs	Induction (I_1)	Induction 2 (I_2)	I_2A	Repeat induction (RI_1)	Consolidation	Maintenance (6 cycles)
Prednisolone (40 mg/m^2)	D 1–28	■	HDAC (2 g/m^2)	Repeat I_1	D 1–7	■
Vincristine (1.4 mg/m^2)	D 1, 8, 15, 22, 29	■			D 1, 15	D 1
L-asparaginase (6,000 U/m^2)	D 2–20, alternate day	■			■	D 1, 3, 5, 7
Daunorubicin (30 mg/m^2)	D 8, 15, 29	■			■	D 1
Mercaptopurine (75 mg/m^2)	■	Daily			D 1–7, 15–21	Start on day 15. Daily, 3 wk out of every 4 wk, for a total of 12 wk
Cyclophosphamide (750 mg/m^2)	■	D 1, 15			D 1, 15	■
Methotrexate (12 mg, IT)	D 1, 8, 15, 22	D 1, 8, 15, 22			■	15 mg/m^2, orally, start on D 15, once a week, missing every 4th wk, for a total of 12 wk
Cranial irradiation (2,000 cGy)	■	10 d			■	■
Cytarabine (70 mg/m^2)	■	■			D 1–3, D 15–17	■

Abbreviations: D, day; HDAC, high-dose cytarabine; IT, intrathecal.
The black squares in the table denote that the drugs (mentioned in Rows) were not given in that particular phase of chemotherapy.

Statistical Analysis

All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) software for windows (IBM Corp., Armonk, NY, United States). The chi-squared test was performed to examine the relation between categorical variables and a value of $p < 0.05$ was considered significant. For survival analysis, Kaplan–Meir survival curves were plotted and log-rank (Mantel–Cox) test was performed; statistical significance ($p < 0.05$), chi-squared values, and mean survival with 95% confidence interval (CI) were calculated.

Ethics: Ethics committee approval was granted for this retrospective study by the Institutional Ethics Committee of Medical College, Kolkata (reference number: MC/KOL/IEC/NON-SPON/2158/07/2023 dated 19.07.2023). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Between June 2009 and August 2013, 156 patients were included in this study after applying the exclusion criteria. Data were analyzed in February 2023. The mean age at presentation was 6.4 ± 0.3 years with a male preponderance of 60.8% ($n = 95$). In total, 109 patients (70%) were precursor B-ALL, of whom 76 (69.7%) were standard risk (pre-B-ALL SR), 22 (20.1%) were intermediate risk (pre-B-ALL IR), and 11 (10%) were high risk (pre-B-ALL HR). In all, 47 (30%) patients had T-ALL, of whom 35 (74.4%) were standard risk (T-ALL SR) and 12 (25.5%) were high risk (T-ALL HR).

Fever was the most common presenting symptom (79.5%), followed by lymphadenopathy (69.8%) and hepatosplenomegaly (52%). Hyperleukocytosis was present in 24 (15%) patients at diagnosis. Approximately 80% were treated in the general pediatric ward and 20% in the oncology ward.

PGR on day 8 was seen in 98 (62.8%) patients. In total, 140 (89.7%) patients achieved remission (<5% blast on bone marrow examination, i.e., M1) at the end of induction and 16 (10.3%) patients died during the induction phase. Twelve of 16 (75%) children who faced induction mortality had a median gap of 2.5 months or more from symptom onset and initiation of treatment. Thirteen of 16 (~81.25%) children who faced induction mortality were suffering from moderate acute malnutrition and 2 (12.5%) were suffering from severe acute malnutrition. Blood culture was positive in approximately 31% ($n = 49$) patients during the course of treatment. The most common organisms isolated in bacterial sepsis were *Klebsiella pneumoniae*, *Pseudomonas* sp., *Staphylococcus aureus*, and enterococci.

►**Tables 3** and **4** depict the frequencies and causes of death during induction, remission death, and EFS according to the risk stratification. The causes of induction death were infection in 10 (62.5%) patients, hemorrhage in 4 (25%) patients, and neurological cause, that is, cortical venous thrombosis in 2 (12.5%) patients. Among infection, bacterial neutropenic sepsis was the most common ($n = 5$, 50%), followed by fungal pneumonia ($n = 3$, 30%), systemic candidiasis ($n = 1$, 10%), and human immunodeficiency virus (HIV) infection ($n = 1$, 10%). Among those who attained remission (89.7%, $n = 140$), relapse occurred in 26% ($n = 27$) precursor B-ALL and 28% ($n = 10$) T-ALL patients. Forty-eight patients (30.7%) died during the postinduction period and the causes of mortality included progressive disease due to relapse in 37 (77%) patients and infection in 11 (22.9%) patients. The commonest cause of overall mortality was progressive disease due to relapse, occurring mostly in the consolidation and maintenance phase. Bone marrow was the commonest site of relapse and observed in 35 (94.6%) patients, followed by testicular relapse in 2 (5%) patients. Bone marrow and testicular relapse occurred at a median gap of 24 and 42 months, respectively, after initiation of treatment. No cases of CNS relapse were seen in our study.

The chi-squared test of independence was performed to examine the relation between risk groups and the incidence of induction mortality. The relation between these variables were significant ($\chi^2 = 82.54$, $p < 0.0001$). However, the chi-squared test of independence between risk groups and incidence of remission death and overall survival was not significant ($\chi^2 = 6.07$, $p = 0.19$). The EFS at 168 months was 59%. Relapse-free survival by Kaplan–Meir analysis (►**Fig. 1**)

Table 3 Details of mortality and event-free survival according to risk-stratified groups

Type of malignancy	Risk stratification	No. of patients ($N = 156$)		No. of deaths during induction ($N = 16$)		Remission death ($N = 48$)		Event-free survival in each group	
		n	%	*n*	%	*n*	%	*n*	%
Pre B-ALL	Pre B-ALL SR	76	48.7	1	6.2	21	43.7	54	71
	Pre B-ALL IR	22	14.1	1	6.2	10	20.8	11	50
	Pre B-ALL HR	11	7.0	3	18.7	5	10.4	3	27
T-ALL	T-ALL SR	35	22.4	1	6.2	11	22.9	23	65
	T-ALL HR	12	7.6	10	62.5	1	2.08	1	8

Abbreviations: B-ALL; B-cell acute lymphoblastic leukemia; HIV, human immunodeficiency virus; HR, high risk; IR, intermediate risk; Pre, precursor; SR, standard risk; T-ALL, T-cell acute lymphoblastic leukemia.

Table 4 Details of mortality during induction according to risk-stratified groups

Risk stratification	No. of patients (*n*)	Cause of induction death	No. of deaths during induction ($N = 16$)	
			n	%
Pre B-ALL SR	76	Cortical venous thrombosis	1	6.2
Pre B-ALL IR	22	Neutropenic sepsis	1	6.2
Pre B-ALL HR	11	Fungal pneumonia	2	12.5
		Neutropenic sepsis	1	6.2
T-ALL SR	35	Neutropenic sepsis	1	6.2
T-ALL HR	12	Hemorrhage	4	25
		Neutropenic sepsis	2	12.5
		Systemic candidiasis	1	6.2
		Fungal pneumonia	1	6.2
		HIV	1	6.2
		Cortical venous thrombosis	1	6.2

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; HIV, human immunodeficiency virus; HR, high risk; IR, intermediate risk; Pre, precursor; SR, standard risk; T-ALL, T-cell acute lymphoblastic leukemia.

was 62.4% for precursor B-cell ALL and 51.1% for T-ALL (log-rank, $\chi^2 = 1.931$, $p = 0.165$). The mean survival for B and T lineages was 111.19 months (95% CI: 97.86–124.51) and 94.36 months (95% CI: 73.04–115.68), respectively.

Discussion and Conclusion

The 5-year survival rate for ALL in the western world is approximately 90% in children younger than 15 years.[11] Compared to the developed world, the biology of ALL appears different in India, with a higher proportion of T-ALL (20–50% as compared to 10–20% in the developed world), hypodiploidy and translocations t (1;19), t (9;22), and t (4;11). All of these factors contribute to a poorer prognosis of leukemia.[1]

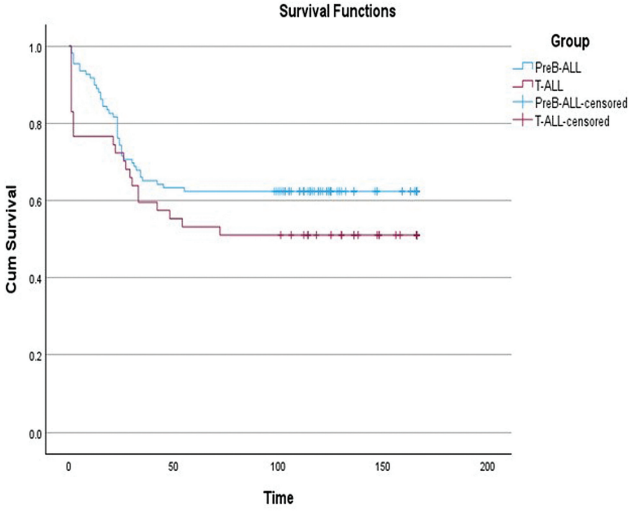

Fig. 1 A Kaplan–Meier survival plot showing relapse-free survival probability for T-cell acute lymphoblastic leukemia (ALL) and B-cell ALL. Cumulative survival (Y axis) has been plotted against time (in months) since diagnosis (X axis).

The incidence of induction mortality was higher in the T-ALL HR group; however, the statistical difference in EFS was not significant between pre-B-ALL SR and T-ALL SR groups treated by the MCP841 protocol. The most common cause of induction death was neutropenic sepsis. Factors such as malnutrition contributed to the increased risk of mortality during the induction period. In the randomized intercontinental trial by Starý et al on intensive chemotherapy for childhood ALL by BFM 2002, PGR was reported in 90.2%,[12] while in a study on outcome of ALL with the ALL-BFM-95 protocol in Nepal by Sharma Poudyal et al, PGR was reported in 71.8% patients.[13] In our study, PGR was reported in 62.8% patients. Out of a total of 64 deaths, most occurred due to relapse in the postinduction period ($n = 37$ [57%] of overall mortality). Bone marrow is the most frequent site of relapse and no CNS relapse was seen. Advani et al obtained similar results for bone marrow relapse, and five patients had a combined bone marrow and CNS relapse.[5] All cases of relapse were advised bone marrow transplant and were referred to institutions with a bone marrow transplant facility. As per the institutional protocol, the cases of relapse were further treated with the St. Jude Protocol and the CCG112 protocol for testicular relapse, but there was no reported survival in cases of relapse in our study.

EFS in our study was 59% at 168 months, which is comparable to the 49% EFS at the end of 5 years reported by Advani et al.[5] In a study by Kapoor et al, relapse-free survival at 5 years was 62% for B-ALL and 28% T-ALL; overall, 53.2% of the patients were in remission at the end of 5 years of starting of treatment.[10] According to the results of randomized intercontinental trial by Starý et al on intensive chemotherapy for childhood ALL by BFM 2002, the 5-year EFS was overall 74% (75% in B-cell precursor and 69% in T cell), 81% in the SR group, 75% in the IR group, and 55% in the HR group.[12] According to a study on outcome of ALL with the

ALL-BFM-95 protocol in Nepal by Sharma Poudyal et al in 2023, the 3-year overall survival and relapse-free survival were 89.4 and 87.3%, respectively. The study undertaken by Sharma Poudyal et al also mentions that the 5-year EFS was 28% in childhood ALL between 1998 and 2012.[13] The higher survival of childhood ALL in recent years, as compared to our study, can be attributed to improving oncological resources over the years, such as enhanced infrastructure and supportive care, awareness among patients, early diagnosis, and specialized training of health care workers.

In spite of its drawbacks, MCP841 using HDAC as a backbone of the protocol is an effective tool for treatment of children suffering from ALL and it has similar survival outcomes in precursor B-ALL and T-ALL. With improving oncological resources, the overall survival has improved in the more recent studies. However, MCP841 remains an important tool in a background of resource-constraint settings and high abandonment. Achieving 50% survival in children with ALL is a challenge in India, and we have reached a comparable survival outcome in par with similar centers in developing countries with the MCP841 protocol. Combating treatment in malnourished children and bridging infections are the major hurdles to improving outcome in developing countries.

Drawbacks

This study is based on a single-center experience, and there is a limitation of available data as it is a retrospective study. Immunophenotyping and cytogenetic reports of all patients could not be procured due to logistic issues and nonavailability of facilities during the time of patient treatment almost two decades ago. Hence, it was not possible to perform a detailed analysis of the correlation between the outcomes based on detailed hematological and cytogenetic reports.

Authors' Contribution

S.B. was responsible for the concept, data acquisition, design of intellectual content, literature search, and manuscript editing. S.S. was responsible for manuscript preparation and literature search. D.R. designed the study. K.D. contributed to manuscript review. M.S. contributed to data analysis and manuscript review. This manuscript has been read and approved by all the authors.

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None.

Conflict of Interest

None declared.

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