Article published online: 2025-09-25

Original Article

Role of Maintenance Therapy with Decitabine in Acute Myeloid Leukemia in First Remission: A Prospective Interventional Study from a Tertiary Care Center in Eastern India

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Ind J Med Paediatr Oncol

Abstract

Introduction Major advances in the diagnostic methodologies and technological progress have led to successful development of many targeted agents in the management of acute myeloid leukemia (AML). At present, standard of care of AML post-remission depends on the molecular risk stratification of the disease. Despite incorporation of newer agents with chemotherapy, relapse remains a major problem. To address this unmet need, many investigators have used hypomethylating and other targeted drugs as maintenance after remission induction in AML in different clinical studies with variable results.

Objectives We conducted this study to determine the efficacy of maintenance decitabine in AML after remission and to assess its side effects.

Materials and Methods This is a prospective interventional study. After considering the inclusion and exclusion criteria, patients with a diagnosis of AML were given 3 + 7 induction. All adverse risk patients were counseled for allogeneic hematopoietic stem cell transplantation and removed from the study if they opted for that. After documenting remission, patients were given three high-dose cytarabine (HIDAC) as consolidation. Those who remain on remission after third HIDAC were started on decitabine maintenance at 12 weeks' interval. A total of 20 patients were included. They were followed up at 3 monthly intervals by complete blood count, peripheral blood smear, and bone marrow aspiration during maintenance. Disease-free survival (DFS) and overall survival (OS) were calculated and compared with historical control. Toxicity and side effects of decitabine were also assessed.

Results At a median follow-up of 29 months, the median DFS and OS were 20.5 and 27.5 months, respectively. Seven patients experienced grade 3 and 1 patient grade 4 hematological adverse events. One patient died due to febrile neutropenia.

Conclusion Decitabine may be considered as safe and effective maintenance agent in AML after achieving first remission.

Keywords
- non-M3 AML
- decitabine
- maintenance
- disease-free and overall survival

Place of study-*Hematology department, Nil Ratan Sirkar Medical College & Hospital (NRSMCH).*

DOI https://doi.org/10.1055/s-0045-1811939.
ISSN 0971-5851.

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

Introduction

Acute myeloid leukemia (AML) is a biologically heterogeneous malignancy of the hematopoietic stem cell (HSC). Major advances in understanding of the disease in recent years include new knowledge about molecular pathogenesis, leading to an update of the disease classification, technological progress in diagnostic methodologies, concept of measurable residual disease (MRD), and successful development of newer drugs such as FLT3, IDH1, IDH2, and BCL2 inhibitors.

The current standard of care for most patients with AML achieving a complete remission (CR) with induction is either chemotherapy or allogeneic hematopoietic stem cell transplantation (Allo-HSCT) depending on the genetic risk stratification of the disease.[1] But Allo-HSCT has its own difficulties in terms of logistics and socioeconomic challenges in this region of our country. Again, frailty and performance status of the eligible patients (by risk stratification) is a limiting factor for Allo-HSCT. Even after doing Allo-HSCT and despite the incorporation of newer therapeutic modalities with intensive chemotherapy, relapse remains a major clinical issue with relapse risk $>$ 50% for all adults with high-risk AML.[1] Given this high rate of relapse, there is urgent need to establish a postremission maintenance therapy to mitigate the risk. Various previous studies using different combinations of chemotherapeutic agents as postremission maintenance failed to show a statistically meaningful improvement in overall outcome of the disease. The EORTC-HOVON trial did not show an improvement in overall survival (OS) with low-dose cytarabine maintenance compared with observation after remission with intensive therapy.[2] In the LAME 89/91 study of pediatric AML, disease-free survival (DFS) was similar in the maintenance (18 months of monthly low-dose cytarabine 25 mg/m^2 twice a day for 4 days and continuous 6-methylprednisone) and observation arms, while OS was inferior in the maintenance arm.[3] Though lenalidomide has beneficial role as maintenance therapy in myeloma, it failed to show statistically meaningful improvement in the outcome for AML.[4] In the realm of immune activation, immune checkpoint inhibitors have shown promising results in Hodgkin lymphoma, Richter syndrome, and in several non hematologic malignancies, but they have been largely disappointing as maintenance therapy in AML.[4] In acute lymphoblastic leukemia (ALL), maintenance has been established as a standard of care because studies consistently show inferior outcomes in ALL without maintenance therapy.[5]

There is no generally accepted definition of "maintenance therapy." Maintenance therapy for AML is defined by the Food and Drug Administration as an extended but time-limited course of treatment, which is less toxic given after achievement of CR with the objective of reducing the risk of relapse.[6]

Considering the continuing poor outcome of AML, there is an urgent need to explore alternative approaches. Hypomethylating agents (HMAs) alone or in combination with other agents have been evaluated in various international studies as maintenance strategies in AML. Decitabine has epigenetic activity and is approved as a chemotherapeutic agent in AML with low toxicities.[7] Many studies in international perspectives have used decitabine as maintenance after remission induction with variable results. But this issue has not been addressed in the Indian scenario. Therefore, we undertook this study to determine whether maintenance therapy with decitabine is beneficial for patients with AML in first remission and also to assess its side effect profiles.

Objective

(1) To assess the effectiveness of maintenance decitabine in AML after attainment of first CR with induction and consolidation
(2) To assess the toxicity and side effect profiles of decitabine

Materials and Methods

Inclusion Criteria

- Diagnosed non-M3 AML patients aged up to 59 years, irrespective of risk groups, not fit/willing for Allo-HSCT
- Patient fit (Eastern Cooperative Oncology Group [ECOG] 0–3) for intensive chemotherapy

Exclusion Criteria

- Pregnancy
- Coexisting renal and liver disease
- Prior azacitidine or decitabine therapy
- AML with myelodysplasia-related gene mutations or myelodysplasia-related cytogenetic abnormalities
- All adverse risk AML patients fit and opted for Allo-HSCT

Study Design

This is a prospective interventional study from May 2021 to December 2023. History taking and clinical examination were done of all patients who were admitted in the hematology ward with a diagnosis of AML. AML was diagnosed based on history, clinical examination, as well as morphology and immunophenotyping of the bone marrow aspirate. Reports of bone marrow aspiration (BMA), cytogenetics, and molecular studies were thoroughly evaluated. Risk stratification was done according to the European LeukemiaNet (ELN) 2017 risk category for AML. Patients were given 3 + 7 induction (cytarabine 100 mg/m^2/day continuous infusion for 7 days and daunorubicin 60 mg/m^2/day for the first 3 days). BMA was done postinduction at D28 or after count recovery to check for disease remission status. All adverse risk group patients are counseled for Allo-HSCT and removed from study if they chose Allo-HSCT as therapy. Other patients in adverse risk category, not eligible for HSCT due to logistic reasons were included in the study. Patients fulfilling the eligibility criteria received three cycles of high-dose cytarabine (HIDAC, 3 g/m^2 over 3 hours, every 12 hours, on days 1, 3, and 5). Post-third HIDAC, BMA was performed again to check for disease remission status.

Patients remaining in CR after consolidation (3rd HIDAC) were enrolled in the study after considering the inclusion

and exclusion criteria. Informed and written consent were obtained. Eligible patients were scheduled to receive eight cycles of decitabine intravenously over 1 hour at 20 mg/m^2 /day for 5 days, every 12 weeks. To be eligible for maintenance, patients were required to have adequate recovery of neutrophils ($>$ 1000/uL) and platelets ($>$ 75000/uL) and be within 60 days of last HIDAC.

Recovery of count is required prior to starting each subsequent cycle of decitabine. If necessary, a 2-week delay before the next cycle of decitabine is permitted to allow count recovery. For grade 4 neutropenia lasting more than 2 weeks or grade 4 thrombocytopenia lasting more than 1 week after decitabine therapy, 1 day of treatment will be deleted from the subsequent cycle. However, a minimum of 3 days of decitabine per cycle will be required to continue protocol therapy. Patients were followed up by clinical examination, complete blood count with peripheral blood smear, and BMA to check for disease remission status.

Disease evaluation time points and follow-up during maintenance included bone marrow examination every 3 months for 2 years after completion of consolidation therapy.

Expected Outcome

Primary outcomes of the study were 1-year DFS, disease relapse, and OS. Secondary outcome were safety and tolerability of decitabine as maintenance therapy.

Criteria for Response and Toxicity

CR was defined as bone marrow cellularity $\geq$ 20% with absolute neutrophil count $> 1 \times 10^9$/L and platelets $> 100 \times 10^9$/L following one or two cycles of induction. The National Cancer Institute Common Toxicity Criteria (CTCAE 5.0) were used to grade adverse events.

DFS is defined as the time from documented CR to time of relapse or death whichever is earlier. OS is calculated as the time from study entry (i.e., prior to induction treatment) to death from any cause. Event-free patients were censored at the time of their last follow-up. DFS and OS are calculated using the methods of Kaplan and Meier statistics and compared with historical control.[8]

Statistical Analysis

Data collected are entered in MS-Excel to make a database. JAMOVI software, version 2.6.26 (free), was used for analysis. Categorical variables are expressed as proportion and percentage and numerical variables as mean and standard deviation. Survival is calculated as per duration of months. DFS and OS are calculated using the Kaplan and Meier method. For statistical significance, unpaired *t*-test is used. A *p*-value of < 0.05 is considered as statistically significant.

Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institute. Ethical clearance from the Institutional Ethics Committee has been taken bearing no. NMC/6672 dated 10/12/2019.

Results

Of the 20 patients registered for the maintenance therapeutic agent decitabine, median age was 23.5 years (range: 4–54 years). Pediatric patients ($<$ 18 years of age) were six and male:female ratio was 3:1.

Seven patients were in the favorable, nine patients in the intermediate, and four patients in the adverse risk group. According to performance status (PS), nine patients were in PS1, seven in PS2, and four in PS3. There were six patients who were *t*(8::21) positive by conventional cytogenetics.

Following table shows the baseline characteristics of the patients (►**Table 1**).

A total of 88 cycles of decitabine were administered (mean: 4.4). Eight patients developed hematological adverse effects (►**Table 2**)—seven patients were grade 3 and one was grade 4. No nonhematological adverse events were noted. One patient died due to febrile neutropenia.

The median follow-up of the surviving patients was 29 months (range: 8–30 months). For the entire treated subjects ($n = 20$), the median OS was 27.5 months with a *30 months'* survival rate of 80%. The median DFS in the group was 20.5 months. Corresponding survival curve (Kaplan–Meier) is shown in ►**Figs. 1** and **2**.

The median OS in pediatric patient was 19.5 months as compared with 28.5 months in adults, while median DFS in pediatric patient was 18.5 months as compared with

Table 1 Baseline characteristics of the study subjects ($N = 20$)

Baseline characteristics	Value
Age (y)	
Median	23.5
Range	4–54
Pediatric patient (number)	6
Sex	
Male	15
Female	5
Ratio	3:1
AML risk category	
Favorable	7
Intermediate	9
Adverse	4
Performance status (PS) (ECOG)	
PS1	9
PS2	7
PS3	4
Conventional cytogenetics	
Normal	8
t(8::21)	6
Others	6

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group.

Table 2 Hematological adverse effects experienced by the patients ($N = 20$)

Grade 3 adverse events	No. of patients	Grade 4 adverse events	No. of patient
Anemia	2	Anemia	0
Neutropenia	3	Neutropenia	1
Thrombocytopenia	2	Thrombocytopenia	0

Note: According to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 5.

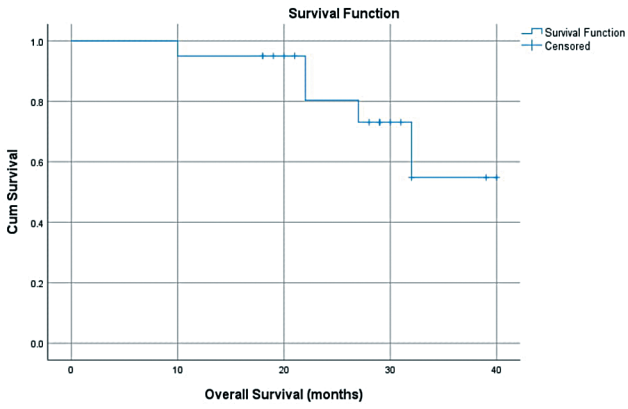

Fig. 1 Overall survival of the patients ($N = 20$).

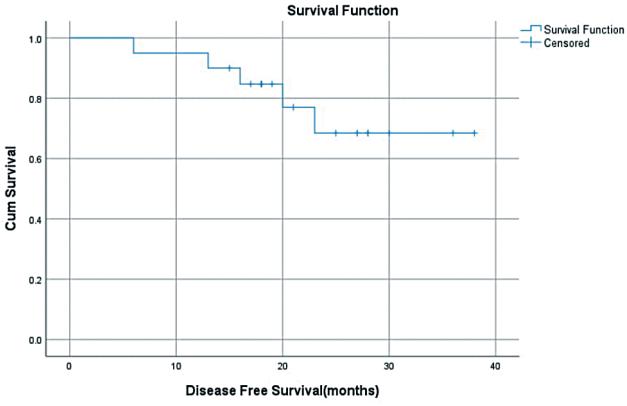

Fig. 2 Disease-free survival of the patients ($N = 20$).

24 months in adults ($p = 0.628$ for both). Women ($n = 5$) were observed to have median OS and DFS of 30 and 23 months, respectively, whereas men ($n = 15$) had OS of 22 months and DFS of 18 months ($p = 0.303$ for both). Mean DFS and OS of the historical control groups were 18.4 and 23.8 months, respectively.[8]

Discussion

It has been shown by previous studies that HMA is well tolerated and has activity as single agent and in combinations in AML and myelodysplastic syndrome, which was the basis for the present study. Therefore, we considered maintenance treatment with decitabine after intensive induction chemotherapy to be a potentially interesting option, especially for patients in CR who are not eligible or fit for Allo-HCT. Furthermore, the azacitidine, due to its hypomethylating mechanism, after conventional chemotherapy, has antileukemic effects that are additive to the effects of chemotherapy. Few studies provided knowledge about the clonal hierarchy and they identified preleukemic HSCs in remission samples, which may survive after exposure to chemotherapy. This concept supports the use of azacitidine and decitabine as maintenance agents in AML.[9] But the beneficial effects of long-term maintenance therapy in AML have not been conclusively established till date. Decitabine and azacitidine may be useful to maintain the remission in AML patients.

Previous studies with HMA are presented below in tabular forms (►**Table 3**).[10–16]

In this prospective interventional study, 20 newly diagnosed AML patients in morphological CR after induction and three cycles of consolidation were given maintenance decitabine at 12 weeks' intervals and followed up. Median DFS and OS were 20.5 and 27.5 months, respectively. Adult patients had better outcome compared with the pediatric group, though statistically insignificant. The most common hematological adverse event in the entire cohort was neutropenia. One patient died of febrile neutropenia.

In our study, we have included newly diagnosed patients of AML irrespective of the ELN 2017 risk category similar to other previously mentioned studies like the ECOG-ACRIN, CALGB 10503, HOVON, and QUAZAR AML-001 trials. This is supported by the fact that core binding factor AML (CBF-AML), despite inclusion in favorable risk category, relapse is a major concern with leukemia-free survival remains at 50 to 60%.[17] In the CALGB 10503 trial described, a sizeable percentage of patients (34%) had CBF-AML and even in them, non-MRD-directed decitabine maintenance did not seem to improve DFS or OS.[11] In another single-arm study from the MDACC, 31 patients with CBF-AML treated with fludarabine-based I-C regimen, decitabine was administered as a maintenance agent in those who had persistent MRD positivity by quantitative polymerase chain reaction or who failed to receive all planned cycles of consolidation. Among 23 patients with MRD at the initiation of maintenance, 12 (52%) attained complete molecular response with a median molecular relapse-free survival of 93 months.[12]

Again, it was not possible from our study to derive which risk category of patients benefitted most from decitabine maintenance owing to less sample size. In the ECOG-ACRIN (E-A) E2906 trial, investigators found there was a significant impact on OS for the FLT3-ITD-negative population, apart

Table 3 Previous studies with HMA as maintenance in AML

Name of study	Study design	Outcome
ECOG-ACRIN (E-A) E2906 trial[10]	120 patients of $\geq$ 60 years with a diagnosis of AML in remission were randomized to decitabine (20 mg/m^2 for 3 days each 4-week cycle for 1 year) or observation after intensive therapy	At a median follow-up period of 50 months after the start of induction therapy, there was no statistically significant difference in DFS or OS between the two arms
CALGB 10503 phase 2 trial[11]	Patients of AML remained in CR postinduction and consolidation were given eight cycles of decitabine IV over 1 hour at 20 mg/m^2/day for 5 days, every 6 weeks for 1 year	For the group that received maintenance decitabine, 1-year DFS and OS were 79% and 96%, respectively. Decitabine maintenance did not provide any apparent benefit for DFS or OS relative to the historical reference group
A single-arm MRD-based study from MD Anderson Cancer Center (MDACC)[12]	31 patients with CBF-AML received maintenance decitabine	The investigators concluded that decitabine can be an effective maintenance for CBF-AML patients with persistent low level MRD after FLAG-based induction regime
HOVON trial: Phase 3 RCT[13]	112 patients $\geq$ 60 years with AML/MDS-excess blasts in CR/CRi after intensive therapy were randomized to receive azacitidine (50 mg/m^2 for 5 days, every 4 weeks for a maximum of 12 cycles) or observation	DFS was significantly improved in the therapy arm (12-month DFS: 64% vs. 42%; $p = 0.04$) with no difference in OS
QUAZAR AML-001 trial: phase 3, randomized, double-blind, placebo-controlled trial of the oral formulation of azacitidine[14]	AML patients $\geq$ 55 years in remission following chemotherapy and not candidate for HSCT were randomly assigned to receive CC-486 (300 mg) or placebo once daily for 14 days per 28-day cycle	Median OS was significantly longer with CC-486 than with placebo (24.7 and 14.8 months, respectively). Median RFS was also significantly longer with CC-486 than with placebo and the benefit were shown in most subgroups defined according to baseline characteristics
AML-342, A Phase II Study of azacitidine and venetoclax as maintenance therapy in AML[15]	This is a phase 2, single-center, single-arm study ongoing since 9/2019. Azacitidine 50 mg/m^2 IV/SQ $\times$5 days and venetoclax 400 mg $\times$14 days or 7 days were administered in 28-day cycles, up to 24 cycles	Out of 34 patients, 9 relapsed and 6 died. The median RFS and OS were not reached. Most common grade ¾ adverse events were thrombocytopenia and neutropenia
GOELMAS trial: Phase II multicentric trial[16]	117 poor-risk AML patients in CR after intensive induction received 12 maintenance cycles alternating every 28 days AZA (sc 75 mg/m^2/d1–7) and Len (10 mg/d1–21)	Median follow-up for survivors was 38 months (26–47). Median OS was 10 months, with 21% 2-year OS. Median CR duration was 7 months (1–30)

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CBF, core binding factor; CR, complete remission; CRi, incomplete count recovery; DFS, disease-free survival; FLAG, fludarabine, cytarabine, G-CSF; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IV, intravenous; Len, lenalidomide; MDS, myelodysplastic syndrome; MRD, measurable residual disease; OS, overall survival; RCT, randomized controlled trial; RFS, relapse-free survival; SQ, subcutaneous.

from improved OS in the decitabine arm compared with observation. In the HOVON trial, though there is improvement in DFS in the azacitidine arm compared with observation (64% vs. 42%), OS did not differ between various treatment groups. Similarly, in other studies also, it could not be conclusively asserted about the most benefitted group according to the molecular risk category.

Conclusion

Outcome of the present study in terms of DFS and OS is comparable or little better compared with the historical control with the reservation of small sample size and absence of control arm. Further studies are needed with larger sample size and longer follow-up period with a control arm to elucidate the effectiveness of decitabine as maintenance agent in AML after attaining first CR.

Patient Consent

Patient consent has been obtained.

Conflict of Interest

None declared.

Acknowledgments

The authors would like to acknowledge the contribution of nursing personnel in indoor and day care center toward data collection and maintaining the demographic records of the patients.

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