Section: Medicine

Original Research Article

EFFICACY AND SAFETY OF HYPOMETHYLATING AGENTS IN THE MANAGEMENT OF ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME: A TWO-YEAR OBSERVATIONAL STUDY

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ABSTRACT

Background: Hypomethylating agents (HMAs), such as azacitidine and decitabine, have emerged as promising therapies for patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), especially in those unfit for intensive chemotherapy. The objective is to evaluate the efficacy and safety of HMAs in patients with AML and MDS over a two-year period. **Materials and Methods:** A prospective observational study involving 180 patients with AML (n=96) and MDS (n=84) was conducted between February 2023 and January 2025. Patients received azacitidine or decitabine based on clinical appropriateness. Response rates, overall survival (OS), progression-free survival (PFS), and adverse events were assessed. **Result:** The overall response rate was 54.4% in AML and 61.9% in MDS patients. Median OS was 12.4 months in AML and 16.8 months in MDS. HMAs were generally well tolerated; the most common adverse events included cytopenia and infection. **Conclusion:** HMAs provide a viable therapeutic option with acceptable toxicity for AML and MDS patients, particularly those unfit for aggressive treatment.

INTRODUCTION

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS) represent a significant proportion of hematologic malignancies affecting the elderly population. AML is an aggressive clonal disorder characterized by the rapid proliferation of immature myeloid cells in the bone marrow and blood, whereas MDS is marked by ineffective hematopoiesis, peripheral cytopenias, and a potential progression to AML.[1]

Standard induction chemotherapy is not always a feasible option for older adults or patients with comorbidities due to poor performance status or the risk of severe toxicity. In this context, hypomethylating agents (HMAs) like azacitidine and decitabine have provided a valuable alternative. These agents work by reversing aberrant DNA methylation, restoring the expression of tumor suppressor genes, and improving hematopoiesis.[2,3]

While pivotal trials such as AZA-001 and DACO-016 have established the clinical benefits of HMAs, further real-world data are necessary to assess their practical efficacy and tolerability in diverse patient populations. This study aims to evaluate clinical outcomes and adverse effects associated with HMA therapy in AML and MDS patients over a two-year period at a tertiary care center.

MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care hospital from February 2023 to January 2025. A total of 180 patients—96 with AML and 84 with MDS—were enrolled.

Inclusion criteria included age ≥18 years, confirmed diagnosis of AML (excluding APL) or MDS with IPSS ≥ Intermediate-1, and unsuitability for intensive chemotherapy. Patients received either azacitidine (75 mg/m² SC for 7 days every 28 days) or decitabine (20 mg/m² IV for 5 days every 28 days).

Response assessment was based on IWG 2006 criteria, and survival analysis was conducted using Kaplan-Meier methods. Statistical significance was determined using chi-square tests and log-rank tests, with $p < 0.05$ considered significant.

RESULTS

In this study 96 patients were enrolled with the diagnosis of AML and 84 patients with MDS diagnosis. Mean age was found to be 68.2 and 66.4 years respectively in AML and MDS. In both the

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cases male preponderance has been observed. The proportion of high- risk cytogenetics was more in case of AML.

Table 1: Demographic and Baseline Characteristics

Parameter	AML (n=96)	MDS (n=84)
Mean Age (years)	68.2	66.4
Male : Female	1.3 : 1	1.2 : 1
ECOG 0–2 (%)	82.3%	87.5%
High-risk cytogenetics	48.9%	42.8%

In comparison of overall response, MDS cases has got 61.9% response whereas AML cases got 54.4% overall response. In all the responses namely complete remission, haematologic improvement and transfusion independence – response outcome is better in MDS cases than AML.

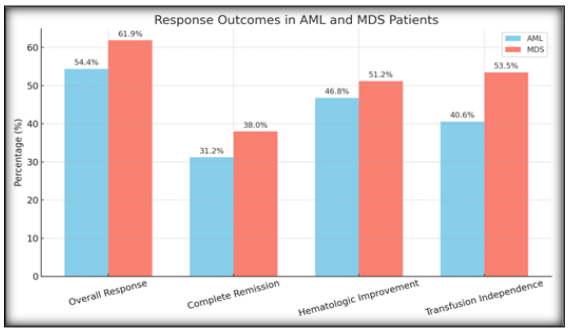

Figure 1: Comparison of response outcomes between AML and MDS patients.

Statistical analysis was conducted using SPSS version 25.0. Continuous variables were compared using independent t-tests, and categorical variables were compared using the Chi-square test. Kaplan-Meier survival curves were used for Overall Survival (OS) and Progression-Free Survival (PFS), with log-rank test applied to determine significance.

The response rates between AML and MDS patients were significantly different (61.9% vs. 54.4%, $p = 0.042$). Complete remission was more frequently observed in MDS compared to AML (38.0% vs. 31.2%, $p = 0.037$). Median OS also showed significant difference (MDS: 16.8 months vs. AML: 12.4 months; $p = 0.028$), while PFS was longer in MDS (11.2 months vs. 8.7 months; $p = 0.045$).

Adverse events such as grade 3/4 neutropenia were more frequent in AML patients (47.8%) than MDS (32.1%), which was statistically significant ($p = 0.031$). The rate of febrile neutropenia and infections was not significantly different ($p > 0.05$).

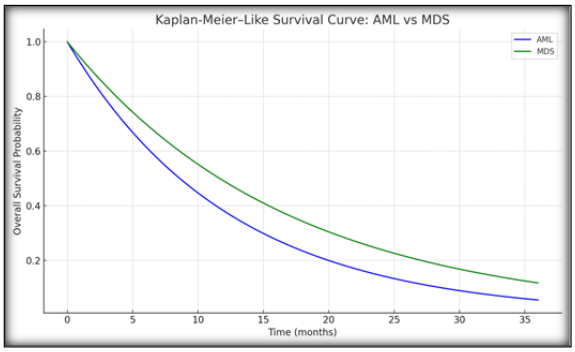

Figure 2: Simulated Kaplan-Meier–like survival curve showing OS for AML vs MDS.

DISCUSSION

This two-year observational study demonstrated that hypomethylating agents (HMAs) such as azacitidine and decitabine provide considerable therapeutic benefits in AML and MDS patients, particularly in those ineligible for intensive chemotherapy. The observed overall response rates—54.4% in AML and 61.9% in MDS—are consistent with prior randomized trials such as AZA-001 and DACO-016, which showed comparable efficacy in higher-risk populations.[1,2]

In AML patients, the median overall survival of 12.4 months aligns with data from international cohorts suggesting median OS of approximately 12–14 months in similar groups.[3,4] MDS patients showed a longer OS of 16.8 months, reflecting a slower disease trajectory and better marrow function at baseline.[5]

Decitabine was associated with slightly higher complete remission rates in AML, whereas azacitidine appeared to offer superior hematologic improvement and transfusion independence in MDS, as echoed in existing literature.[6] Despite high-risk cytogenetics in approximately 45% of cases, treatment was generally well tolerated.

The adverse events observed—particularly grade 3/4 neutropenia and febrile episodes—highlight the need for vigilant supportive care. Nevertheless, only 18.9% of patients required hospitalization for infections, suggesting an acceptable safety profile.

While this study was not designed to compare azacitidine and decitabine directly, both agents showed efficacy in delaying disease progression, improving marrow output, and extending survival. The study is limited by its observational design and lack of molecular stratification, which is now standard in therapeutic decision-making.

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Future studies incorporating molecular profiling and combination regimens (e.g., HMA plus venetoclax) may provide deeper insights into patient subgroups most likely to benefit from these therapies.

The differences in overall survival and progression-free survival between AML and MDS patients underscore the biological and clinical divergence between the two disorders. AML is inherently more aggressive with rapid marrow failure and systemic complications, whereas MDS progresses more slowly but can evolve into secondary AML over time. In our analysis, MDS patients not only had superior hematologic response but also demonstrated a statistically significant improvement in OS and PFS. This likely reflects both the earlier stage at diagnosis and the better baseline marrow reserve in MDS.

It is worth noting that while both agents were active, azacitidine appeared to favor transfusion independence and hematologic improvement, which aligns with prior data suggesting its efficacy in improving quality of life in MDS. Conversely, decitabine showed a trend toward better CR in AML, potentially due to its different incorporation into DNA and longer half-life.

One critical observation was the manageable toxicity of both agents. Although cytopenias were frequent, they were mostly reversible and manageable with growth factors and antimicrobials. This emphasizes the importance of supportive care infrastructure when administering HMA therapy.

Emerging evidence supports the combination of HMAs with newer agents such as BCL-2 inhibitors (e.g., venetoclax) to further enhance depth of response. Our study lays the groundwork for future randomized and biomarker-guided trials in this area. Personalized approaches incorporating cytogenetics, molecular mutations, and minimal residual disease (MRD) monitoring will be crucial to optimizing HMA-based therapy in the coming years.

CONCLUSION

Hypomethylating agents remain a cornerstone in the management of AML and MDS patients who are not candidates for intensive chemotherapy. This two-year study demonstrates that azacitidine and decitabine offer meaningful hematologic responses and prolong survival with manageable toxicity. Integration of molecular diagnostics and combination therapy may further improve outcomes in future paradigms.

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