Comparative Efficacy and Safety of Oral Azacitidine (CC-486) Versus Injectable Hypomethylating Agents as Maintenance Therapy Following Allogeneic Haematopoietic Cell Transplantation in Myelodysplastic Neoplasms: A Systematic Review and Network Meta-Analysis

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INTRODUCTION

Relapse remains the leading cause of treatment failure after allogeneic haematopoietic cell transplantation (alloHCT) in myelodysplastic neoplasms (MDS). Hypomethylating agents (HMAs) are used as post-transplant maintenance therapy to lower relapse risk through antileukaemic and immunomodulatory effects.
No meta-analysis has directly compared oral azacitidine (CC-486) with injectable HMAs in this setting, and high-quality, MDS-specific evidence has remained limited.

AIM

To systematically review and compare, via network meta-analysis, the efficacy and safety of oral azacitidine (CC-486) versus injectable hypomethylating agents as maintenance therapy after alloHCT in patients with myelodysplastic neoplasms, focusing on relapse-free and overall survival.

METHOD

We systematically searched electronic databases for studies enrolling adults with MDS undergoing alloHCT who received post-engraftment HMA maintenance.

Primary outcomes were relapse-free survival (RFS) and overall survival (OS), pooled as hazard ratios (HRs) using random-effects meta-analysis (DerSimonian–Laird).

Secondary outcomes included cumulative incidence of relapse, non-relapse mortality, acute and chronic graft-versus-host disease (GVHD), and treatment discontinuation.

Risk of bias was assessed with Cochrane RoB 2.0 and ROBINS-I, evidence certainty was graded using GRADE, and network consistency was tested with the global Wald test.

CONCLUSIONS

HMA maintenance after alloHCT significantly improves survival and reduces relapse in MDS, with a favourable impact on chronic GVHD and non-relapse mortality.

CC-486 shows the most promising relapse-free survival estimate in indirect comparison, but superiority over injectable agents cannot be confirmed without head-to-head randomised evidence from trials such as AMADEUS (NCT04173533).

RESULTS

Twenty-five studies (n=5,847) — 3 randomised trials and 22 cohort studies — evaluated five maintenance strategies: CC-486, injectable azacitidine, injectable decitabine, oral decitabine/cedazuridine, and observation.

Pooled HMA maintenance significantly improved relapse-free survival (HR 0.77, 95% CI 0.66–0.89) and overall survival (HR 0.79, 95% CI 0.67–0.92) versus observation, with an even stronger effect in MDS-specific subgroups (RFS HR 0.72, 95% CI 0.56–0.92).

By NMA P-score, CC-486 ranked highest for RFS benefit, followed by injectable decitabine and injectable azacitidine, though cross-agent comparisons were entirely indirect.

HMA maintenance also significantly reduced chronic GVHD (RR 0.78, P=0.005) and non-relapse mortality (RR 0.78, P=0.02), without increasing acute GVHD.

25
studies included

5,847
patients (n)

5
treatment nodes compared

Outcome	Comparison	Effect estimate	95% CI / P	GRADE
RFS	HMA vs Observation	HR 0.77	0.66–0.89	Moderate
OS	HMA vs Observation	HR 0.79	0.67–0.92	Moderate
RFS (MDS subgroup)	HMA vs Observation	HR 0.72	0.56–0.92	Moderate
RFS (NMA)	CC-486 vs Observation	HR 0.62	0.42–0.91	Low
RFS (NMA)	Inj. decitabine vs Observation	HR 0.72	—	Low
RFS (NMA)	Inj. azacitidine vs Observation	HR 0.79	—	Low
Chronic GVHD	HMA vs Observation	RR 0.78	P=0.005	Moderate
Non-relapse mortality	HMA vs Observation	RR 0.78	P=0.02	Moderate
Acute GVHD	HMA vs Observation	No significant difference	—	—

GRADE certainty was moderate for overall RFS/OS benefit and for decitabine-specific chronic GVHD reduction, but low for CC-486 superiority, pending the phase 3 AMADEUS trial (NCT04173533).

ACKNOWLEDGEMENTS

The authors thank the Department of Medicine, Government Medical College Kozhikode, for institutional support. No external funding was received for this study.

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