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Outcome After Hypomethylating Agents Failure in Patients With IDH1 Mutated Myelodysplastic Syndromes

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INTRODUCTION

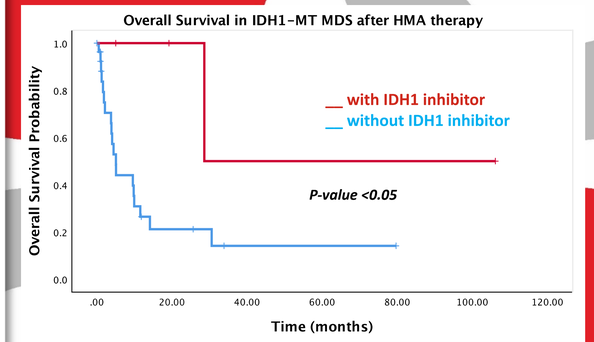
- Patients with higher-risk myelodysplastic syndromes (MDS) typically have poor outcomes after hypomethylating agent (HMA) failure, with a median overall survival (OS) of 4-6 months.
- Recently, ivosidenib was approved for relapsed and refractory *IDH1* mutant MDS, demonstrating a median OS of 3 years in a small cohort of patients.

METHOD

- We retrospectively analyzed the outcomes of a large cohort of MDS patients treated with frontline HMA therapy at Moffitt Cancer Center.
- Our study aimed to compare outcomes between *IDH1*-mutant (MT) and wild-type (WT) patients and to assess the impact of *IDH1* inhibitor use in real-world settings after HMA failure.

RESULTS

- A total of 1,057 MDS pts received frontline HMA therapy with majority were classified as higher-risk by IPSS-M.
- *IDH1* mutations were detected in 32 pts (3%), with the R132C mutation being the most common (50%).
- Co-mutations of *EZH2* (12.5% vs. 4.6%), *DNMT3A* (37.5% vs. 0.1%), and *CBL* (6.3% vs. 2%) were more frequent in *IDH1*-MT cases, whereas *ASXL1* co-mutations (22.7% vs. 6.3%) were more common in *IDH1*-WT cases.
- The upfront HMA regimens included azacitidine (61.5%), decitabine (14.4%), oral decitabine (1.5%), HMA with venetoclax (11.1%), and other HMA combinations (11.5%).
- CR rates to HMA therapy were similar between *IDH1*-MT and *IDH1*-WT (16% vs. 14%, P=0.78).
- Following HMA therapy failure, the median OS was 10 months: 9.6 months for *IDH1*-MT and 10.3 months for *IDH1*-WT patients.
- Four *IDH1*-MT patients received *IDH1* inhibitors post-HMA failure (ivosidenib, n=3; olutasidenib, n=1), showing a significantly improved median OS of 28.6 months compared to 5.1 months for those who did not receive *IDH1* inhibitors (P<0.05).



CONCLUSIONS

- Although HMA therapy response rates are similar for *IDH1*-MT and *IDH1*-WT MDS patients, the historical median OS for *IDH1*-MT MDS after HMA failure without *IDH1* inhibitor is poor.
- *IDH1* inhibitors significantly improve survival in *IDH1*-MT patients in real world data.

REFERENCES

- DiNardo CD, Roboz GJ, Watts JM, et al. Final phase I substudy results of ivosidenib in patients with mutant IDH1 relapsed/refractory myelodysplastic syndrome. *Blood Adv*. Published online April 19, 2024. doi:10.1182/bloodadvances.2023012302

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