Single-Center Experience with Frontline *IDH* Inhibitor Therapy in *IDH*-Mutated MDS

A. Azem[1], N. Al Ali[1], S. Kareem[1], E. Padron[1], O. Chan[1], A. Kuykendall[1], J. Lancet[1], R. Komrokji[1], D. A. Sallman[1]

1. Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, Fl, USA

Introduction

Mutations in isocitrate dehydrogenase (*IDH*) genes occur in ~5% of adult patients with myelodysplastic syndromes (MDS)[1]. While their prognostic significance is controversial, a Mayo Clinic study associated mutated *IDH1* MDS with adverse outcomes[2]. Targeted *IDH* inhibition has shown promise in MDS. Ivosidenib, an *IDH1* inhibitor, is approved for relapsed/refractory (R/R) mutant *IDH1* MDS after a phase 1 reporting a CR of 38.9%, OR of 83.3%, mOS of 35.7 months, and 68.6% probability of CRs lasting ≥5 years[3]. Enasidenib, an *IDH2* inhibitor, is being studied in a phase II trial with azacitidine for high-risk MDS. Neither have been studied in the frontline setting.

Objective

Present our experience using *IDH* inhibitors as frontline therapy for MDS at Moffitt Cancer Center.

Design

From our database (Jan2017–July2024), we identified 10 patients with either *IDH1* (n=8) or *IDH2* (n=2) mutations treated with frontline *IDH* inhibitors, as monotherapy (n= 7) or with a hypomethylating agent (n=3).

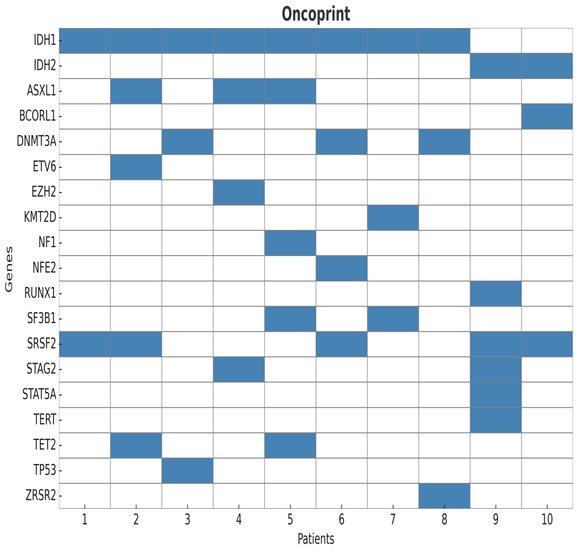
Baseline Characteristics	
Median Age	68
No. Males	4
No. Caucasians	9
No. of pts with co-mutations	10
Median no. of co-mutations	3 (1-6)
Median % of BM blasts	2.5% (1-8%)
No. ≥2 cytopenia	8

Risk	IPSS-R No.	IPSS-M No.
Very low	1	0
Low	3	4
Mod. Low	0	2
Intermediate	4	0
High	0	2
Mod. High	0	1
Very high	2	1

WHO 2022	No.
MDS with low blasts	4
MDS with low blasts and SF3B1 mutation	2
MDS with EB-1	3
hypoplastic MDS	1

Results

- Overall response rate (ORR) was 100% per IWG 2023 criteria, with 70% achieving CR or CR-equivalent.
- Median time to best response per IWG 2023 was 14 days (range: 8–223), median therapy duration was 27 months (range:11–67+).
- Two patients had major molecular responses (≥50% reduction in *IDH* allele burden), and five achieved complete molecular responses (undetectable IDH mutations).
- At analysis, nine patients were alive; seven maintained response and continued therapy, while two underwent allogeneic stem cell transplant and remain in CR.
- One patient lost response after 12 months on ivosidenib, with persistent *IDH* mutation and acquisition of an *ETNK1* mutation. He was treated with second-line olutasidenib, which was complicated by AKI and differentiation syndrome requiring treatment hold. He passed away from disease progression.



Conclusion

Our experience indicates that frontline *IDH* inhibitor therapy has robust and durable clinical activity that appears superior versus the historical experiences in the R/R-MDS population, supporting consideration of early intervention in *IDH*-mutant patients. These data support the ongoing randomized PyramIDH study comparing frontline ivosidenib to azacitidine in *IDH*-mutant patients and early phase trials evaluating *IDH* inhibition in patients with *IDH*-mutant CCUS.

References

1. Medeiros, B.C., et al., Isocitrate dehydrogenase mutations in myeloid malignancies. Leukemia, 2017. 31(2): p. 272–281.
2. Patnaik, M.M., et al., Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic study of 277 patients. Leukemia, 2012. 26(1): p. 101–5.
3. DiNardo, C.D., et al., Final phase 1 substudy results of ivosidenib for patients with mutant IDH1 relapsed/refractory myelodysplastic syndrome. Blood Adv, 2024. 8(15): p. 4209–4220.

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