Genomic Insights into Myelodysplastic Syndrome: Uncovering Understudied Mutations

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Introduction

Mutations in EZH2, KRAS, EGFR, and several other genes are established drivers and therapeutic targets in various malignancies[1]. Their prevalence and clinical relevance in myelodysplastic syndrome (MDS), however, is not well characterized. In this study, we examine the frequency of these mutations in MDS, laying the groundwork for future therapeutic exploration.

Methods

We conducted a descriptive study using data from the Myelodysplastic Syndromes International Working Group (MDS IWG) used for developing Molecular International Prognostic Scoring System (IPSSM), published in NEJM Evidence 2022 (cBioPortal) on patients with MDS2-5. The analysis was limited to a single distinct sample per patient to avoid duplication. Mutations were categorized as driver or Variant of Unknown Significance (VUS).

Results

A total of 3,323 patients with MDS were identified, with one sample per patient. Mutation frequencies were as follows: EZH2 mutations in 243 cases (7.3%) with total 295 total mutations (253 driver, 42 VUS); NF1 mutations in 188 cases (5.7%) with 233 total mutations
(163 driver, 70 VUS); NRAS mutations in 179 cases (5.4%) with 207 total mutations (200 driver, 7 VUS); KRAS mutations in 128 cases (3.9%) with 138 total mutations (133 driver, 5 VUS); BRAF mutations in 34 cases (1%) with 34 total mutations (22 driver, 12 VUS); EGFR mutations in 10 cases (0.3%) with 10 total mutations (10 driver, 0 VUS). Mutations with frequency >1.5% were considered significant and of these significant mutations, all were somatic mutations. There was a higher % of patients in the altered subgroup classified as high or very high risk according to IPSS-M, 23.64% and 30.68% vs 12.6% and 14.77% respectively.

Target mutation	Altered cases	Altered %
EZH2	243	7.3
NF1	188	5.7
NRAS	179	5.4
KRAS	128	3.9
BRAF	34	1
EGFR	10	0.3

Table 1. Prevalence of target gene alterations in MDS (N = 3,323). "Altered cases" = patients with ≥1 mutation in the specified gene; "Altered %" = patient-level prevalence (cases ÷ 3,323).

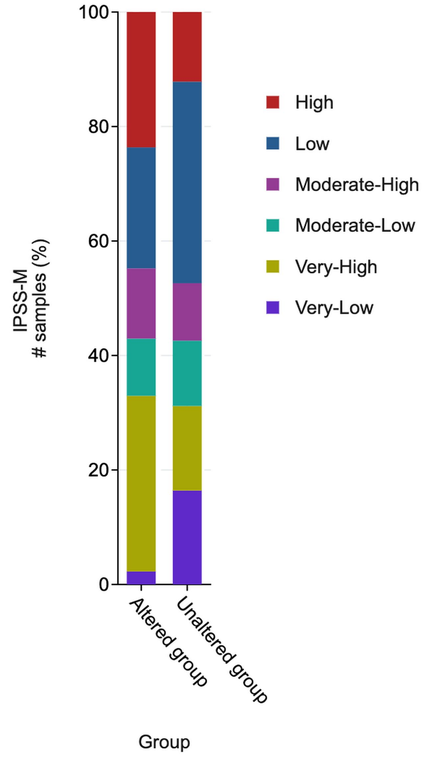


Figure 1. IPSS-M risk distribution by genomic alteration status. 100% stacked bars show the proportion of IPSS-M categories in patients with any target mutation ("Altered") versus none ("Unaltered"). The altered group is enriched for higher-risk disease: **High 23.64% vs 12.60%** and **Very-High 30.68% vs 14.77%** in unaltered.

Discussion

In this study, we identified that MDS, as a clonal disorder, may harbor additional mutations for which FDA-approved targeted therapies are available. Our findings highlight actionable mutations such as EZH2, NF1, and KRAS, which can be potentially treated with agents like tazemetostat, selumetinib, and sotorasib. For patients with MDS, especially high and very high risk, outcomes after relapse remain poor, often revealing undruggable oncogenic drivers, like NRAS. The high prevalence of these mutations underscores the need for clinical trials evaluating these inhibitors in the relapsed/refractory setting, offering new treatment options for patients with limited alternatives.

References

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