IDH mutations are enriched in myelodysplastic syndrome patients with severe neutropenia and can be a potential for targeted therapy

Myelodysplastic syndromes (MDS) are a heterogenous group of neoplastic bone marrow failure diseases.[1] The Revised International Prognostic Scoring System (IPSS-R) is the most widely used prognostic scoring system to tailor therapy for MDS patients. The IPSS-R incorporated severe neutropenia (SN) defined as absolute neutrophil count (ANC) <0.8x10^9/L as a prognostic variable. Among MDS patients (pts), 18% had ANC <0.8x10^9/L.[2] Current treatment guidelines recommend considering hypomethylating agents or immunosuppressive therapy for treating MDS pts with neutropenia with low neutrophil response reported in clinical studies (<10-20%).[3] Recurrent infections remain a major cause of morbidity and mortality in MDS pts.[1] Identification of the genomic landscape of MDS pts with SN is crucial given the large unmet clinical need in this patient population which may assist identifying potential targeted therapy.

IDH somatic mutations (MT) are described in 8-12% of acute myeloid leukemia (AML) cases and MDS.[4,5] These recurrent MT in key metabolic enzymes lead to the production of the oncometabolite 2-hydroxyglutarate (2-HG), which promotes leukemogenesis through a block in normal myeloid differentiation. Selective oral inhibitors of mutant *IDH1* and *IDH2* have subsequently been developed and are now approved for AML[4] and are under investigation for MDS.[6,7]

We analyzed all MDS pts treated at Moffitt Cancer Center with known ANC values around time of diagnosis and who had next-generation sequencing (NGS) as part of routine clinical care using standard Illumina platform as previously described.[8] We defined SN around time of diagnosis for the purpose of this study according to the IPSS-R cut-off (ANC 0.8x10^9/L) and stratified pts into two groups based on this definition.

We identified 1,972 MDS pts among whom 466 pts (24%) had SN. Table 1 summarizes baseline characteristics comparing SN and non-SN pts. Neutropenic pts were slightly younger, had higher myeloblasts percentage, lower platelet counts, higher risk disease and were more likely to be classified as MDS-EB subtypes. Ninety-three pts had isolated SN (hemoglobin [Hgb] >10 g/dL and platelets >100x10^9/L).

IDH MT (*IDH-1/IDH-2*) were the only MT observed at higher rate among neutropenic pts. Figure 1A summarizes landscape of common MT observed comparing SN and non-SN pts in the whole group and stratified by IPSS-R (lower risk defined as very low to intermediate and higher risk as high and very high groups). Among the whole cohort, 13% of MDS pts (61/462) with SN harbored *IDH* MT compared to 6% in non-SN pts (85/1,489) (P<0.005). Both *IDH-1* and *IDH-2* MT were more common in SN pts and among both lower and higher risk IPSS-R groups. The most common observed hot spot in *IDH-2* was R140, although the R172 hotspot was observed more in SN pts. Among pts with isolated SN, 18% harbored *IDH* MT compared to 12% in non-isolated SN (P=0.1). *IDH-1* MT were more common in pts with isolated SN (11% *vs.* 4%; P=0.01) but no difference in *IDH-2* MT (8% in both isolated SN and non-isolated SN groups; P=0.8). *TP53* was observed in 26% compared to 19% respectively for SN and non-SN pts, P<0.005 but no statistical difference was observed when examined among IPSS-R risk groups.

Figure 1B illustrates the presence of SN among MT and wild-type (WT) commonly observed somatic MT in MDS pts. Among pts with *IDH1/2* MT 42% of pts had SN compared to 22% among WT, 40% *IDH-1* MT MDS pts had SN compared to 23% of *IDH-1* WT, and 44% of *IDH-2* MT had SN compared to 23% of *IDH-2* WT. SN was present in 30% of *TP53* MT MDS pts compared to 23% among those with WT. *SF3B1* MT MDS pts were less likely to have SN. The median overall survival (mOS) was shorter (25 months [mo] *vs*. 42 mo; P<0.005) and the rate of AML transformation higher (49% *vs*. 26%; P<0.005) in SN *versus* non-SN pts respectively. SN was not associated with worse outcome when adjusted for myeloblast percentage, (hazard ratio [HR]: 1.0; 95% confidence interval [CI]: 0.83-1.2; P<0.98). The mOS was worse for SN *IDH* WT compared to non-SN *IDH*-WT, (24 mo *vs.* 43.5 mo; P<0.005). This observation reflects enrichment of *TP53* MT among SN *IDH*-WT (29%) compared to non-SN *IDH* WT (8%) (P=0.001). There was no difference in mOS comparing SN *IDH*-MT compared to non-SN *IDH* MT (mOS 33 mo *vs*. 30 mo; P=0.3). Among SN pts, there was no difference in mOS among *IDH* MT compared to WT (mOS 33 mo *vs.* 24 mo; P=0.1). Among non-SN pts *IDH*-MT was associated with worse OS with a mOS 31 mo compared to 42 mo for non-SN *IDH*-WT (P=0.04) in univariable analysis. In multivariable analysis adjusting for IPSS-R, *IDH* MT in non-SN pts was not statistically significantly associated with worse outcome (HR: 1.3; P=0.08)

The complete response rate (CR) to azacitidine was 20% among SN pts. There was no difference in response to

Table 1. Baseline characteristics comparing neutropenic and non-neutropenic myelodysplastic syndromes patients.

	Severe neutropenia (ANC <0.8x10^9/L) N=466	No severe neutropenia (ANC ≥0.8x10^9/L) N=1,506	*P* value
Age in years, mean	67.6	69	0.001
Sex (male), N (%)	292 (63)	950 (63)	0.9
Race (white), N (%)	415 (89)	1,371 (92)	0.15
t-MDS, N (%)	92 (20)	275 (18)	0.47
WHO classification MDS SLD/MLD, % MDS SLD/MLD RS, % MDS-EB, % AML <30% blasts, % del 5q, % MDS-U, % MDS/MPN, % MDS-RS-T, %	 21 4 52 21 1 1 0 0	 33 16 29 6 4 2 6 4	<0.005
R-IPSS Very low, % Low, % Intermediate, % High, % Very high, %	 4 11 17 23 45	 16 36 18 14 16	<0.005
Myeloblasts, % Hgb g/dL, mean Platelets x10^9/L, mean ANC x10^9/L, mean WBC x10^9/L, mean	12 9.4 98 0.46 2.2	6 10 147 3.2 6	<0.005 0.1 <0.005 <0.005 <0.005

t-MDS: therapy-related myelodysplastic syndrome; WHO: World Health Organization; SLD: single lineage dysplasia; MLD: multilineage dysplasia; RS: ring sideroblasts; EB: excess blasts; AML: acute myeloid leukemia; MDS-U: MDS unclassifiable; MPN: myeloproliferative neoplasm; MDS-RS-T: MDS-RS with thrombocytosis; R-IPSS: Revised International Prognostic Scoring System; Hgb: hemoglobin; ANC: absolute neutrophile count; WBC: white blood cell.

azacitidine among SN pts based on *IDH MT* status (CR rates 20% [n=51/254] for *IDH*-WT and 15% [n=5/33] for *IDH*-MT; *P*=0.9).

Given the lack of effective treatment options for neutropenia in general, two symptomatic *IDH1* SN lower risk MDS pts have been treated with ivosidenib. The first pt had *IDH1* R123 C (variant allele frequency [VAF] 44%) and *SRSF2* P95R (VAF 43%). Hemoglobin improved from 9.4 g/dL to 14 g/dL, platelets were normal at baseline. There were 1-2% circulating peripheral blood blasts which resolved on therapy. The pt has been in remission for 31 months. The second pt had *DNMT3A* and *IDH1* R132 C mutations at baseline (VAF at 7% for both). Platelets improved from 111x10^9/L to 180x10^9/L. Hgb also improved from 11.8 g/dL to 14.1 g/dL. The pt has been in durable remission for 11 months now. Both pts achieved a complete hematologic response within 2 weeks of initiation of therapy (ANC 0.3 to 2.8 and ANC 0.21 to 2.4), which has been durable, with therapy ongoing.

Severe neutropenia is present in almost one fourth of MDS pts and it is associated with worse outcome.[2] SN is more commonly observed with higher-risk disease, complex karyotype and excess myeloblasts. SN is less encountered in lower-risk MDS which may dictate choice of therapy and isolated neutropenia as sole indication for treatment in lower-risk MDS is even more rare.[9] There are limited options for treating neutropenia.[9] Granulocyte colony stimulating factors have not been shown to improve outcomes.[10] Anti-thymocyte globulin/cyclosporine may yield trilineage response including neutrophil response in selected subset of young or hypoplastic lower-risk MDS but is rarely utilized.[11] Hypomethylating agents, widely used to treat patients with bi/pancytopenia, only yield up to 20% neutrophil response compared to 19% with conventional care regimens.[12]

We observed that *IDH* MT are enriched among SN MDS pts regardless of IPSS-R risk group. Notably, in two of two *IDH-1* MT SN pts, treatment with ivosidenib resulted in ongoing, durable complete hematologic responses.

The *IDH* MT genotype and the neutropenia phenotype association have been observed in patients with AML. *IDH* mutations were also commonly observed among patients

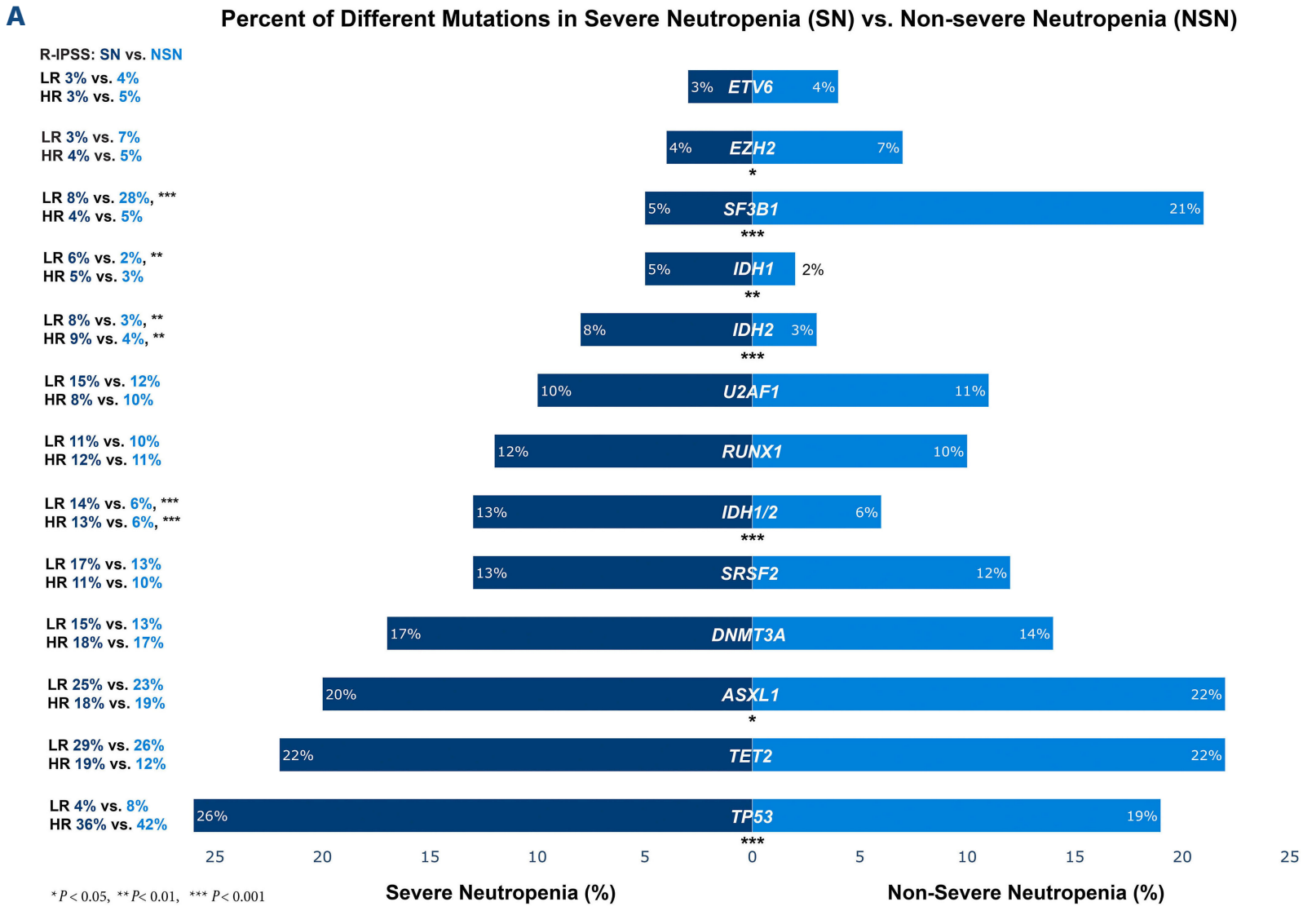

Figure 1. Correlation of somatic mutations and severe neutropenia among myelodysplastic syndromes patients. (A) Somatic mutations among patients with severe neutropenia compared to non-severe neutropenia and (B) frequency of severe neutropenia among commonly observed somatic mutations in myelodysplastic syndromes patients. LR: low risk; HR: high risk.

with chronic idiopathic neutropenia and evidence of clonal hematopoiesis.[13] Potentially, treatment early on in disease course may lead to higher response rates, particularly in the absence of other driver co-mutations.

Patnaik *et al*. reported *IDH* MT in 12% of MDS patients There was no difference in ANC based on *IDH* MT status. Patients with *IDH-1* MT had a lower white blood cell count and were all red blood cell transfusion dependent. *IDH-1* but not *IDH-2* mutation in multivariable analysis was associated with inferior OS and LFS.[5]

The molecular IPSS was recently proposed to refine the IPSS-M prognostic utility and incorporate molecular data. Notably, the new molecular model excluded neutropenia as a clinical variable.[14] A new personalized precision model using artificial intelligence retained neutrophil count as a clinical variable but did not include *IDH* MT.[15]

Early promising data using *IDH* inhibitors in MDS were reported in different setting including post hypomethylating agent failure higher-risk disease, first-line higher-risk MDS as single agent and in lower risk after erythroid stimulating agents' failure.[6,7] Responses were reported in 50% of lower-risk MDS patients treated with *IDH* inhibitors after erythroid stimulating agents failure.

Our study limitation includes its retrospective nature, not fully examining the co-occurrence of somatic mutations and the interplay with other clinical variables. The underlying biology of this observation (likely differentiation block or inhibition of dioxygenase enzymes) for MDS pts with neutropenia should be further explored. IDH inhibitors through reduction of 5-HG and promotion of differentiation may improve granulopoiesis. Our data demonstrating enrichment of *IDH* MT among MDS pts with SN and the anecdotal durable responses observed in two cases of lower risk MDS with SN merit further exploring this targeted therapy in the context of clinical trials.

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Contributions

RK designed the study, analyzed data and wrote the manuscript; NA collected and analyzed data; OC, KS, AK, JL and EP reviewed, edited and approved the final version of the manuscript and contributed patients; DS designed the study, reviewed the manuscript and contributed patients.

Data-sharing statement

No data will be shared.

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