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

by Rami Komrokji, Najla al Ali, Onyee Chan, Kendra Sweet, Andrew Kuykendall, Jeffrey Lancet, Eric Padron, and David A. Sallman

Received: July 4, 2022.
Accepted: November 11, 2022.

Citation: Rami Komrokji, Najla al Ali, Onyee Chan, Kendra Sweet, Andrew Kuykendall, Jeffrey Lancet, Eric Padron, and David A. Sallman. IDH mutations are enriched in myelodysplastic syndrome patients with severe neutropenia and can be a potential for targeted therapy. Haematologica. 2022 Nov 24. doi: 10.3324/haematol.2022.281607 [Epub ahead of print]

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
IDH mutations are enriched in myelodysplastic syndrome patients with severe neutropenia and can be a potential for targeted therapy

Rami Komrokji, Najla al Ali, Onyee Chan, Kendra Sweet, Andrew Kuykendall, Jeffrey Lancet, Eric Padron and David A. Sallman

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

Corresponding author:

Rami Komrokji, MD
Professor of Oncologic sciences
Senior Member
H Lee Moffitt Cancer Center
12902 Magnolia Drive, Tampa, FL 33612
Rami.komrokji@moffitt.org

Key words: Myelodysplastic syndromes, MDS, neutropenia, IDH mutations

Words count: 1462
Tables :1
Figures: 1

Authors’ contributions
RK study design, data analysis and write manuscript
NA data collection, data analysis
OC,KS,AK, JL, EP review, editing, patient contribution and final approval
DS study design, manuscript review, patient contribution

Data sharing statement:
No data shared
Myelodysplastic syndromes (MDS) are a heterogenous group of neoplastic bone marrow failure diseases. 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) < 0.8 x10^9 /L as a prognostic variable. Among MDS patients (pts), 18% had ANC < 0.8 x10^9 /L. Current treatment guidelines recommend considering hypomethylating agents or immunosuppressive therapy for treating MDS patients (pts) with neutropenia with low neutrophil response reported in clinical studies (<10-20%). Recurrent infections remain a major cause of morbidity and mortality in MDS pts. 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 are described in 8-12% of acute myeloid leukemia (AML) cases and MDS. These recurrent mutations 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 and under investigation for MDS.

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. We defined SN around time of diagnosis for the purpose of this study according to the IPSS-R cut off (ANC 0.8 x10^9 /L) and stratified pts into two groups based on this definition.
We identified 1972 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 (Hgb > 10 g/dl and platelets > 100 x10^9 /L).

*IDH* mutations (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 (85/1489) (p < .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=.1). *IDH-1* MT were more common in pts with isolated SN (11% vs 4%; p=.01) but no difference in *IDH-2* MT (8% in both isolated SN and non-isolated SN groups, p=.8). *TP53* was observed in 26% compared to 19% respectively for SN and non-SN pts, p <.005 but no statistical difference was observed when examined among IPSS-R risk groups.

Figure-1 B illustrates presence of SN among MT and wild type (WT) commonly observed somatic mutations 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 < .005) and the rate of AML transformation higher (49% vs 26%; p < .005) in SN vs non-SN pts respectively. SN was not associated with worse outcome when adjusted for myeloblast percentage, HR 1.0 (95% CI 1.83-1.2) (p = .98). The mOS was worse for SN *IDH WT* compared to non-SN *IDH-WT*, (24 versus 43.5 mo, p < .005). This observation reflects enrichment of *TP53* MT among SN *IDH-WT* (29%) compared to non-SN *IDH WT* (8%) (p = .001). There was no difference in mOS comparing SN *IDH-MT* compared to non-SN *IDH MT* (mOS 33 vs 30 mo; p = .3). Among SN pts, there was no difference in mOS among *IDH MT* compared to WT (mOS 33 vs 24 mo; p = .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 = .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 = .08).

The complete response rate (CR) to azacitidine was 20% among SN pts. There was no difference in response to 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 = .9).

Given 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 (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 PB blasts which resolved on therapy. 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 111 to 180. Hgb also improved from 11.8 g/dl to 14.1 g/dl. 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 $IDH$ mutations are enriched among SN MDS pts regardless of IPSS-R risk group. Notably, in 2 of 2 $IDH-1$ 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 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 absolute neutrophil count based on $IDH$ MT status. Patients with $IDH-1$ MT had lower WBC 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.  

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. A new personalized precision model using artificial intelligence retained neutrophil count as a clinical variable but did not include $IDH$ MT.

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. 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 2 cases of lower risk MDS with SN merit further exploring this targeted therapy in the context of clinical trials.
References:

<table>
<thead>
<tr>
<th></th>
<th>Severe Neutropenia (ANC &lt; 0.8x10^9/L) n=466</th>
<th>No severe neutropenia (ANC ≥ 0.8x10^9/L) N=1506</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean</strong></td>
<td>67.6</td>
<td>69</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>292 (63%)</td>
<td>950 (63%)</td>
<td>.9</td>
</tr>
<tr>
<td><strong>Race (white)</strong></td>
<td>415 (89%)</td>
<td>1371 (92%)</td>
<td>.15</td>
</tr>
<tr>
<td><strong>t-MDS</strong></td>
<td>92 (20%)</td>
<td>275 (18%)</td>
<td>.47</td>
</tr>
<tr>
<td><strong>WHO classification</strong></td>
<td></td>
<td></td>
<td>&lt; .005</td>
</tr>
<tr>
<td>MDS SLD/MLD</td>
<td>21%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>MDS SLD/MLD RS</td>
<td>4%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>MDS-EB</td>
<td>52%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>AML &lt; 30% blasts</td>
<td>21%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Del5 q</td>
<td>1%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>MDS-U</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>0</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>MDS-RS-T</td>
<td>0</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td><strong>R-IPSS</strong></td>
<td></td>
<td></td>
<td>&lt; .005</td>
</tr>
<tr>
<td>Very low</td>
<td>4%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>17%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>23%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>45%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td><strong>Myeloblasts %</strong></td>
<td>12%</td>
<td>6%</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Hgb (g/dl), mean</td>
<td>9.4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Platelets (10^9/L), mean</td>
<td>98</td>
<td>147</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>ANC, mean</td>
<td>.46</td>
<td>3.2</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>WBC, mean</td>
<td>2.2</td>
<td>6</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>
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 MDS patients.