A Classification of Myelodysplastic Syndromes That Aids Clinical Decision-Making

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Disclosures

• No potential conflict of interest to disclose
• No discussion of off-label uses
Classification is the Language of Medicine

• Classification is the language of medicine: diseases must be described, defined, and named before they can be diagnosed, treated, and studied

Cazzola. Blood. 2016 May 19;127(20):2361-4
The Classification Schism in Hematopathology

2022:
• International Consensus Classification
• WHO-5
The Molecular Revolution in MDS

2009: Somatic mutation of TET2 in myeloid malignancies (NEJM. 2009;360:2289-3019)

2022: Genomic landscape of MDS (NEJM Evid 2022;1:7)

9254 oncogenic mutations across 121 genes
The Impact of Next-Generation Sequencing on Diagnosis, Classification, and Prognostication of Myeloid Malignancies

Conservatives (morphology)

vs

Progressives (genomics)

MDS with Ring Sideroblasts

MDS with Ring Sideroblasts: Prognostic Relevance of Morphology

Myelodysplastic Syndrome with Ring Sideroblasts

Clinical Significance of SF3B1 Mutation in MDS

Overall survival

Leukemia-free survival

Clinical Significance of \textit{SF3B1} Mutation in MDS with Ring Sideroblasts

\textbf{Overall survival} \hspace{2cm} \textbf{Leukemia-free survival}

\textbf{A} \hspace{2cm} \textbf{B}

Malcovati et al Blood. 2015 Jul 9;126(2):233-41
Mutational Landscape of MDS with Ring Sideroblasts

Mutational Landscape of MDS with Ring Sideroblasts: Clinical Correlates

Somatic mutation in SF3B1 (~80% of MDS patients with ring sideroblasts)

A benign disorder mainly characterized by ineffective erythropoiesis and isolated anemia, with a low risk of leukemic transformation.

Somatic mutation in SRSF2

A subtype of MDS with ring sideroblasts with poor prognosis.

Somatic mutation in TP53 (multi-hit state)

A subgroup of MDS with ring sideroblasts with very poor outcomes.

No otherwise specified

A heterogeneous subgroup of MDS patients with ring sideroblasts.
Molecular Taxonomy of MDS and Its Clinical Implications

• 3,233 treatment-naive patients with MDS or related neoplasms

• Gene mutations, CNAs, and cnLOH events were derived from targeted capture DNA sequencing of a 152-gene panel enriched with genome-wide CNA probes

Bernard et al. 2023
## Molecular Taxonomy of MDS and Its Clinical Implications

<table>
<thead>
<tr>
<th>Molecular subgroup</th>
<th>Median overall survival (years)</th>
<th>Risk of leukemic transformation</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with no recurrent genetic event</td>
<td>&gt;8</td>
<td>Very low</td>
<td>Non clonal disorder</td>
</tr>
<tr>
<td>SF3B1-mutant MDS</td>
<td>&gt;5</td>
<td>Low</td>
<td>Ring sideroblasts, anemia responsive to luspatercept</td>
</tr>
<tr>
<td>ZRSR2-mutant MDS</td>
<td>&gt;5</td>
<td>Low</td>
<td>Male patients</td>
</tr>
<tr>
<td>Molecularly NOS MDS</td>
<td>&gt;4</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>CCUS-like MDS</td>
<td>&gt;4</td>
<td>Low</td>
<td>Cytopenia related to clonal hematopoiesis</td>
</tr>
<tr>
<td>MDS with del(5q)</td>
<td>&gt;4</td>
<td>Low</td>
<td>Responsive to lenalidomide</td>
</tr>
<tr>
<td>MDS with biallelic TET2 mutation</td>
<td>&gt;4</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>DDX41-mutant MDS</td>
<td>2-4</td>
<td>High</td>
<td>Potential germline predisposition</td>
</tr>
<tr>
<td>U2AF1-mutant MDS (37)</td>
<td>2-4</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>U2AF1-mutant MDS (154)</td>
<td>2-4</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>SRSF2-mutant MDS</td>
<td>2-4</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>BCOR/L1-mutant MDS</td>
<td>2-4</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>IDH-STAG2-mutant MDS</td>
<td>0-2</td>
<td>High</td>
<td></td>
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<tr>
<td>MDS with t(1;7)</td>
<td>0-2</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>-7/SETBP1-mutant MDS</td>
<td>0-2</td>
<td>High</td>
<td></td>
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<tr>
<td>EZH2-ASXL1-mutant MDS</td>
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<td>High</td>
<td></td>
</tr>
<tr>
<td>ASXL1-mutant MDS</td>
<td>0-2</td>
<td>Very high</td>
<td>Poorly responsive to any currently available treatment</td>
</tr>
<tr>
<td>TPS3-complex MDS</td>
<td>0-2</td>
<td>Very high</td>
<td></td>
</tr>
</tbody>
</table>

Bernard et al. 2023
SF3B1-Mutant MDS
SF3B1-Mutant Myeloid Neoplasms

Bernard et al. 2023
Conclusions

• Genomic profiling allows the identification of MDS molecular subgroups associated with distinct clinical phenotypes and outcomes.

• Developing a classification of MDS based on genomic classes may significantly benefit clinical decision-making.