Low Risk Myelodysplastic Syndromes (MDS)

Tiffany Tanaka, MD
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Diagnosis
Bone Marrow Biopsy

cancer.gov (National Cancer Institute website)
Diagnoses that look like MDS (but aren’t!)

**Benign Causes**
- Medications
- HIV
- EBV
- Hep B/C
- Autoimmune Disorders
- Hepatic or Renal Disease
- Alcohol Abuse
- Vitamin Deficiencies
- Copper Deficiency
- Iron Deficiency

**Non-Benign (“Clonal”) Causes**
- Immune Injury
- CMML
- JMML
- aCML
- MDS/MPN-RS-T
- MDS/MPN-U
- AA
- PNH
- hMDS
- Inherited BMF
- CCUS
- CHIP
- sAML
- AML-MRC
- SM-AHN
- MPN
- SM
- Abnormal Proliferation

Bejar, Curr Hematol Malig Rep 2015
Tanaka, Bejar, Blood 2019
How MDS affects patients

• Low blood counts
• Increased bleeding, infection, anemia
• One-third of patients develop acute myeloid leukemia (AML)

Changes in Cell Shape

<table>
<thead>
<tr>
<th>Pseudo-Pelger anomaly</th>
<th>Ring sideroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple separated nuclei</td>
<td>Myeloblasts</td>
</tr>
</tbody>
</table>

Chromosome Changes

- 50% of patients

DNA Changes (mutations)

- 90% of patients

Cazzola et al, *Blood* 2013

ASH Image Bank – James Vardiman
# MDS subtypes (based on bone marrow)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)(^c)</td>
<td>Single or bicytopenia</td>
<td>Dysplasia in ≥10% of one cell line, &lt;5% blasts(^d,2)</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
<td>Anemia, no blasts</td>
<td>≥15% of erythroid precursors w/ ring sideroblasts, or ≥5% ring sideroblasts if SF3B1 mutation present</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
<td>Cytopenia(s), &lt;1 x 10^9/L monocytes</td>
<td>Dysplasia in ≥20% of cells in ≥2 hematopoietic lineages, &lt;15% ring sideroblasts (or &lt;5% ring sideroblasts if SF3B1 mutation present)</td>
</tr>
</tbody>
</table>

**MDS patients have “dysplasia” in greater than 10% of bone marrow cells, and less than 20% blasts (leukemia cells)**

| MDS, unclassifiable (MDS-U)                                   | Cytopenias, ±1% blasts on at least 2 occasions | Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts |
| MDS with isolated del(5q)                                    | Anemia, platelets normal or increased          | Unilineage erythroid dysplasia, isolated del(5q), <5% blasts ± one other abnormality except -7/del(7q) |
| Refractory cytopenia of childhood (Provisional WHO category)  | Cytopenias, <2% blasts                      | Dysplasia in 1–3 lineages, <5% blasts |

What is my MDS stage?
International Prognostic Scoring System, Revised (IPSS-R)

1. Hemoglobin
   Red Blood Cells
2. Absolute Neutrophil Count
   Type of White Blood Cell
3. Platelet Count
   Clotting Cells
4. Bone Marrow Blasts
   Leukemia Cells
5. Chromosome Abnormalities

• Very Low Risk
• Low Risk
• Intermediate Risk
• High Risk
• Very High Risk
Example Patient

Margie is a 78-year-old woman with:

- **Hemoglobin**: 8.2 g/dL
- **Neutrophils**: 2.3 x 10⁹/L
- **Platelet**: 240 x 10⁹/L

Bone marrow biopsy shows:

- **Blasts**: 1%
- **Chromosomes**: Normal

The lower the score, the better!
Lower Risk = Better Survival

Genetic Variation of MDS


Haferlach et al, *Leukemia* 2014
### Genes Mutations in MDS

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes</th>
<th>Overall Incidence</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td>20%–25%</td>
<td>Associated with normal karyotypes. More frequent in CMML (40%–60%). Common in Clonal hematopoiesis of indeterminate potential (CHIP) and Clonal cytopenia of undetermined significance (CCUS).</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td>12%–18%</td>
<td>More frequent occurrence in AML, particularly R882 mutations. Common in CHIP and CCUS.</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Nonsense or Frameshift</td>
<td>15%–25%</td>
<td>Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (40%–50%). Common in CHIP and CCUS.</td>
</tr>
<tr>
<td>EZH2</td>
<td>Nonsense or Frameshift</td>
<td>5%–10%</td>
<td>Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).</td>
</tr>
<tr>
<td>SFB3B</td>
<td>Missense: E662, Y802, R626, N626, H662, T663, K668, R706, H704, G740, G742, D781</td>
<td>20%–30%</td>
<td>Strongly associated with ring sideroblasts and more frequent in MDS-RS (80%). Independently associated with a more favorable prognosis.</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Missense or In-Frame Deletion involving codon P65</td>
<td>10%–15%</td>
<td>More frequent in CMML (40%) and associated with a poor prognosis.</td>
</tr>
</tbody>
</table>

**Gene mutations may aid the diagnosis of MDS, and may also predict survival**

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<th>Mutated Gene</th>
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<tr>
<td>MPL</td>
<td>Missense: W515L/K</td>
<td>&lt;5%</td>
<td>Observed in MDS/MPN-RS&amp;T where it can occur in conjunction with SFB3B mutations.</td>
</tr>
<tr>
<td>ETV6</td>
<td>Nonsense or Frameshift</td>
<td>&lt;5%</td>
<td>Independently associated with a poor prognosis.</td>
</tr>
<tr>
<td>GATA2</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td>Missense in codons 349–356</td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>DOX41D</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td>Missense in codon R526H</td>
<td>Constitutional (germline) mutations in this gene can occur.</td>
</tr>
<tr>
<td>IDH1</td>
<td>Missense: R132</td>
<td>&lt;5%</td>
<td>More frequent in AML.</td>
</tr>
<tr>
<td>IDH2</td>
<td>Missense: R1400, R172</td>
<td>&lt;5%</td>
<td>More frequent in AML. Associated with a poor prognosis.</td>
</tr>
<tr>
<td>SETBP1</td>
<td>Missense: E865, T864, L865, D868, S869, G870</td>
<td>&lt;5%</td>
<td>Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).</td>
</tr>
<tr>
<td>PTPN1</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td>&lt;5%</td>
<td>More frequent in cases with excess blasts, but no association with survival.</td>
</tr>
<tr>
<td>BCR</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td>&lt;5%</td>
<td>Associated with a poor prognosis. More frequent in CMML (5%–10%).</td>
</tr>
<tr>
<td>FLT3</td>
<td>Internal Tandem Duplication or Missense: in codon D835</td>
<td></td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>WTI</td>
<td>Nonsense or Frameshift or Splice Site</td>
<td></td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>NPM1</td>
<td>Frameshift: W286fs*12</td>
<td></td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td>STAT3</td>
<td>Missense: any codons 564–674</td>
<td>&lt;5%</td>
<td>Occurs in large granular lymphocyte leukemia (LGL) associated with MDS; associated with immune bone marrow failure.</td>
</tr>
<tr>
<td>PPM1D</td>
<td>Nonsense or Frameshift</td>
<td>~5%</td>
<td>Associated with therapy-related MDS, but not associated with adverse prognosis independent of TP53. Common in CHIP and CCUS.</td>
</tr>
</tbody>
</table>
Treatment
**General Approach**

- **Priorities in low-risk MDS**
  1. Improvement of cytopenia(s)
  2. Less transfusions
  3. Less iron overload
  4. Tolerability of a given treatment
  5. Quality of life
  6. Delay disease progression
  7. Improve survival
  8. Cure

- **Priorities in high-risk MDS**
  1. Delay disease progression
  2. Improve survival
  3. Cure
  4. Reduction of disease burden
  5. Improvement of cytopenia(s)
  6. Less transfusions
  7. Tolerability of a given treatment
  8. Quality of life

Platzbecker et al, *Blood* 2019
Treatments for Low Risk MDS

- Close Monitoring
- Supportive Treatment: Blood transfusions, Iron chelation
- Erythropoiesis stimulating agents (ESA)
- Lenalidomide for del(5q)
- Luspatercept for MDS-RS Subtype
- Hypomethylating Agents (Azacitidine, Decitabine) might be considered
- Immunosuppressive Therapy (ATG, Cyclosporine) in select situations
Treating Anemia

- **Anemia Only**
  - **Mild**: Observe
  - **Moderate/Severe**
    - Del(5q) Only: Lenalidomide
    - No Del(5q), Check Epo Level
      - Less than 500: Epo (ESA)
      - 500 or more: Luspatercept
  - If no improvement, Luspatercept
Erythropoiesis-Stimulating Agents (ESA)

- Epoetin Alfa or Darbepoietin
- Stimulate red blood cell production
- Subcutaneous injections every 1-2 weeks
- Side effects: headache, joint pain, high blood pressure, thrombosis (rare)

Patients with Epo level below 200 have better responses that last longer

Fenaux et al. *Leukemia* 2018
Lenalidomide

- Lower-risk MDS with del(5q)
- Oral (pill)
- 70% of patients no longer require transfusions
- 50% of patients experience “cytogenetic response,” where the del(5q) abnormality is no longer found
- Side effects: Low blood counts, nausea, diarrhea, fatigue, itching
Luspatercept

- Lower-risk MDS with ring sideroblasts (MDS-RS)
- No response to ESA or Epo level above 500
- Subcutaneous injection every 3 weeks
- 38% of patients no longer required transfusions after 6 months
- Side effects: Low back pain, fatigue, nausea, diarrhea, dizziness

Acceleron Pharma
More than anemia?

Thrombocytopenia, Neutropenia, or Bone marrow blasts

- Supportive Treatments
- Hypomethylating Agents (Azacitidine, Decitabine)
- Immunosuppressive Therapy

If favorable response, continue until progression
No response: Clinical trial or bone marrow transplant
Hypomethylating (HMA) Therapy

- Azacitidine, Decitabine
- IV, SQ (*oral decitabine-cedazuridine)
- Blood counts initially worsen, more transfusions needed
- Slow responses in most (4-6 months)
- Treatment schedule
  - Azacitidine day 1-7, every 28 days
  - Decitabine day 1-5, every 28 days
- Side effects: nausea, constipation, worsened blood counts

Fenaux et al. *Lancet Oncol* 2009
THANK YOU!

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Soo Park MD

UCSD Research Team
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Brian Reilly PhD
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OUR PATIENTS!

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