What is MDS? How Do We Determine Prognosis?

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Associate Member, FHCRC
Associate Professor, UWMC
Synopsis

• What is MDS?
  – Bone marrow stem cell problem
  – Difficulties in Diagnosis
  – Pathogenesis
  – Epidemiology

• Classification and Prognosis
  – WHO classification
  – R-IPSS Prognosis
  – Cancer Genomics
megaloblastoid changes (arrows) and cytoplasmic changes (discontinuous arrow) is poorly reproducible
Granulated blast cells (arrows) makes the distinction between blast cells and promyelocytes (discontinuous arrow) difficult.
Bone Marrow Failure Syndromes

MDS Pathogenesis

Stage 1
Intrinsic increase in apoptotic response and inflammation
↑ TNFα-induced apoptosis
↑ ROS
Induction of homeostatic mechanisms
Stem cell depletion

Stage 2
Acquisition of anti-apoptotic molecules
↑ Bcl-2
Expansion
Emergence of abnormal clones with point mutations in NRas and AML1
Telomere erosion and senescence
Impaired immunosurveillance by NK and T cells

Stage 3
Initiation of clonal evolution
Abnormalities in DNA repair mechanisms with propagation of abnormal cells

Abnormal ribosomes
Altered MP localization
Stromal cell defects
Altered T-cell homeostasis
Inflammatory microenvironment

Bone marrow

Suppressed hematopoiesis
Molecular model of MDS progression
High risk for leukemia transformation

MDS: Epidemiology

- 9,700 new cases/year in US (Adults)
- More common than AML
- Median survival 2-3 years
- Disease burden likely underestimated
- Predominantly a disease of the elderly
  - Median age > 70
  - Incidence males > females
  - Incidence ↑ with age

Rollison et al. Blood. 2008;112:45-52
Greenberg et al. Blood 1997; 89:2085-
Age-Related Incidence of MDS

Age-specific incidence rates (per 100,000)

- Less than 50: 0.5
- 50-59: 5.3
- 60-69: 15
- 70-79: 49
- 80 and over: 89

Classification & Prognosis
<table>
<thead>
<tr>
<th>Name</th>
<th>Dysplastic lineages</th>
<th>Cytopenias*</th>
<th>Ring sideroblasts as % of marrow erythroid elements</th>
<th>BM and PB blasts</th>
<th>Cytogenetics by conventional karyotype analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)</td>
<td>1</td>
<td>1 or 2</td>
<td>&lt;15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia (MDS-MLD)</td>
<td>2 or 3</td>
<td>1-3</td>
<td>&lt;15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td><strong>MDS with ring sideroblasts (MDS-RS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MDS-RS with single lineage dysplasia (MDS-RS-SLD)</td>
<td>1</td>
<td>1 or 2</td>
<td>≥15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS-RS with multilineage dysplasia (MDS-RS-MLD)</td>
<td>2 or 3</td>
<td>1-3</td>
<td>≥15%/&lt;5%†</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any, unless fulfills all criteria for MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>1-3</td>
<td>1-2</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>del(5q) alone or with 1 additional abnormality except −7 or del (7q)</td>
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<tr>
<td><strong>MDS with excess blasts (MDS-EB)</strong></td>
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<td></td>
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<tr>
<td>MDS-EB-1</td>
<td>0-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM 5%-9% or PB 2%-4%, no Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>MDS-EB-2</td>
<td>0-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM 10%-19% or PB 5%-19% or Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td><strong>MDS, unclassifiable (MDS-U)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with 1% blood blasts</td>
<td>1-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM &lt;5%, PB = 1%, no Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>with single lineage dysplasia and pancytopenia</td>
<td>1</td>
<td>3</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>based on defining cytogenetic abnormality</td>
<td>0</td>
<td>1-3</td>
<td>&lt;15%§</td>
<td>BM &lt;5%, PB &lt;1%, no Auer rods</td>
<td>MDS-defining abnormality</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>1-3</td>
<td>1-3</td>
<td>None or any</td>
<td>BM &lt;5%, PB &lt;2%</td>
<td>Any</td>
</tr>
</tbody>
</table>

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10⁹/L; and absolute neutrophil count, <1.8 × 10⁹/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10⁹/L.
†If SF3B1 mutation is present.
‡One percent PB blasts must be recorded on at least 2 separate occasions.
§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

WHO Criteria: MDS

**Minimal Morphologic Criteria**
- ≥10% of the cells in at least one lineage must show dysplasia
- Dysplasia not required if defining cytogenetic abnormal present, BM blasts ≥ 5%, PB blasts ≥ 2%, or Auer rods
- At least one cytopenia* present
- Causes of secondary dysplasia^ must be excluded

**Presumptive Diagnosis**

<table>
<thead>
<tr>
<th>Unbalanced</th>
<th>Balanced</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7 or del(7q)</td>
<td>t(11;16)(q23;p13.3)</td>
<td>Complex karyotype (≥ 3 abnormalities)</td>
</tr>
<tr>
<td>-5 or del(5q)</td>
<td>t(3;21)(q26.2;q22.1)</td>
<td></td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>t(1;3)(p36.3;q21.1)</td>
<td></td>
</tr>
<tr>
<td>-13 or del(13q)</td>
<td>t(2;11)(p21;q23)</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>inv(3)(q21q26.2)</td>
<td></td>
</tr>
<tr>
<td>del(9q)</td>
<td>t(6;9)(p23;q34)</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10^9/L; and absolute neutrophil count, <1.8 × 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10^9/L

^Hypothyroidism, Vit B 12 deficiency, Cu level, ETOH use

Cancer Genomics

Mutation discovery/Clonality

- Cytogenetics
- Candidate gene sequencing
- Whole Genome Sequencing (unbiased comprehensive platform)

Patient care

- diagnosis
- risk stratification
- therapy

Abnormal

Normal
# IPSS and Comprehensive Cytogenetic Scoring System

<table>
<thead>
<tr>
<th>Classification / Prognostic Group</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
</tr>
<tr>
<td><strong>IPSS</strong></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>Normal; -Y; del(5q); del(20q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Other</td>
</tr>
<tr>
<td>Poor</td>
<td>7*</td>
</tr>
<tr>
<td><strong>5-Group</strong></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>-Y; del(11q)</td>
</tr>
<tr>
<td>Good</td>
<td>Normal; del(5q); del(20q); del(12p)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q); +8; i(17q); +19; any other</td>
</tr>
<tr>
<td>Poor</td>
<td>-7; Inv(3)/t(3q)/del(3q)</td>
</tr>
<tr>
<td>Very poor</td>
<td>—</td>
</tr>
</tbody>
</table>

* Any chromosome 7 abnml
† number of clonal abnml

## Revised IPSS (IPSS-R)

<table>
<thead>
<tr>
<th>points</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>blasts ( %)</td>
<td>&lt;2%</td>
<td>-</td>
<td>2-4%</td>
<td>-</td>
<td>5-10%</td>
<td>&gt;10%</td>
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<tr>
<td>Hemoglobin</td>
<td>&gt;10 g/dl</td>
<td>8-10 g/dl</td>
<td>&lt;8 g/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ANC</td>
<td>&gt;0.8 G/l</td>
<td>&lt;0.8 G/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td>&gt;100</td>
<td>50-100</td>
<td>&lt;50</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Very Good</th>
<th>Good</th>
<th>Intermed</th>
<th>Poor:</th>
<th>Very Poor</th>
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</thead>
<tbody>
<tr>
<td>-Y del(11q)</td>
<td>Normal</td>
<td>-7/7q</td>
<td>der3q(21)</td>
<td>der3q(26)</td>
<td>Complex</td>
</tr>
<tr>
<td>der(1;7)</td>
<td>+8</td>
<td>der3q(26)</td>
<td>Complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(5q)</td>
<td>Iso(17q)</td>
<td>Double</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(20q)</td>
<td>+19</td>
<td>inclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(12p)</td>
<td>+21</td>
<td>7q/7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double incl</td>
<td>other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(5q)</td>
<td>double inclusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

- 4 categories
- 3 categories
- 2 categories
- 3 categories
- 5 categories
- 16 subgroups

Table 3. IPSS-R Prognostic Score Values

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤2</td>
<td>&gt;2-&lt;5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
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</table>

Table 4. IPSS-R Prognostic Risk Categories/Scores

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>RISK SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>≤1.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3-4.5</td>
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<tr>
<td>High</td>
<td>&gt;4.5-6</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;6</td>
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</tbody>
</table>

Clonal evolution model

840 mutations

Founding clone

Subclone

STAG2

PTPN11, RUNX1

MDS

2° AML

Walter et al, NEJM 2012
Survival by Mutational Abnormalities in MDS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZH2</td>
<td>Univariate model</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Model with adjustment for IPSS</td>
<td>&lt;0.001</td>
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<tr>
<td>TP53</td>
<td>Univariate model</td>
<td>&lt;0.001</td>
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<td></td>
<td>Model with adjustment for IPSS</td>
<td>&lt;0.001</td>
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<tr>
<td>RUNX1</td>
<td>Univariate model</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Model with adjustment for IPSS</td>
<td>&lt;0.001</td>
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<tr>
<td>ASXL1</td>
<td>Univariate model</td>
<td>0.004</td>
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<td>Model with adjustment for IPSS</td>
<td>0.006</td>
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<td>ETV6</td>
<td>Univariate model</td>
<td>0.05</td>
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<td></td>
<td>Model with adjustment for IPSS</td>
<td>0.04</td>
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<td>CBL</td>
<td>Univariate model</td>
<td>0.02</td>
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<td>Model with adjustment for IPSS</td>
<td>0.05</td>
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<td>NRAS</td>
<td>Univariate model</td>
<td>0.008</td>
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<td>Model with adjustment for IPSS</td>
<td>0.17</td>
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<td>DH2</td>
<td>Univariate model</td>
<td>0.03</td>
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<td>Model with adjustment for IPSS</td>
<td>0.17</td>
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<td>TET2</td>
<td>Univariate model</td>
<td>0.57</td>
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<td>Model with adjustment for IPSS</td>
<td>0.50</td>
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<tr>
<td>IDH2</td>
<td>Univariate model</td>
<td>0.82</td>
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<tr>
<td></td>
<td>Model with adjustment for IPSS</td>
<td>0.52</td>
</tr>
<tr>
<td>IDH1</td>
<td>Univariate model</td>
<td>0.53</td>
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<td>Model with adjustment for IPSS</td>
<td>0.17</td>
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<td>KRAS</td>
<td>Univariate model</td>
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<td>0.86</td>
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<td>NPM1</td>
<td>Univariate model</td>
<td>0.99</td>
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<tr>
<td></td>
<td>Model with adjustment for IPSS</td>
<td>0.97</td>
</tr>
</tbody>
</table>


Spliceosome mutations in 85% of MDS

Frequency of gene mutations differ in MDS vs. AML

* FDR<0.05
Clinical Presentation

• Asymptomatic

• Symptoms related to low blood counts
  – Anemia (fatigue, SOB, DOE, angina, CHF)
  – Infection (principal cause of death)
  – Bleeding (petechiae, ecchymosis, epistaxis, hemorrhage)
## Diagnostic Evaluation: Peripheral Blood

<table>
<thead>
<tr>
<th>Diagnostic Study</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with Differential &amp; Platelet Count,</td>
<td>Evaluate for cytopenias, peripheral blasts</td>
</tr>
<tr>
<td>Reticulocyte Count</td>
<td></td>
</tr>
<tr>
<td>Serum Fe, TIBC, Ferritin, Folic Acid, B12</td>
<td>Evaluate for other possible causes of anemia</td>
</tr>
<tr>
<td>LDH, Haptoglobin, Reticulocyte Count, Coombs</td>
<td>Evaluate for possible underlying hemolysis</td>
</tr>
<tr>
<td>Serum Erythropoietin</td>
<td>Baseline to determine role for growth factor</td>
</tr>
</tbody>
</table>

## Diagnostic Evaluation: Bone Marrow

<table>
<thead>
<tr>
<th>Diagnostic Study</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirate</td>
<td>Evaluate for morphologic abnormalities. Used for flow, cytogenetics, FISH</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Evaluate cellularity &amp; presence of fibrosis</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Evaluate for <em>non-random</em> chromosomal abnormalities. Examine 20 metaphases. &gt; 2 = non-random event</td>
</tr>
</tbody>
</table>

Bone Marrow Findings

• Myelodysplastic Syndromes (MDS)
  – Usually hypercellular, although can be hypocellular
  – Dysplasia involving at least 10% of any single cell line
  – Characteristic cytogenetic findings
  – Excess Blasts ($\geq 5\%$)
  – Ringed sideroblasts (RARS)
  – CD 34 + cells $>0.5\%$
Figure 2. Hypocellular MDS may be confused with Aplastic Anemia

Maslak, P. ASH Image Bank 2004;2004:101115
Figure 1. A Prussian Blue histochemical stain of a bone marrow aspirate of a patient with myelodysplastic disorder, refractory anemia with ringed sideroblasts, is shown.
Figure 3. Ringed sideroblast, myelodysplastic syndromes (MDS), shown with a Prussian blue stain at low power
Figure 1. Dysplastic megakaryocytes
Figure 1. Dysplastic erythroid precursor has open chromatin and basophilic cytoplasm
Figure 8. This figure summarizes the characteristic findings associated with MDS with an isolated del(5q) syndrome
Pseudo Pelger-Huet cell

Ringed Sideroblasts

Megaloblastoid Anemia

Hypolobated Micromegakaryocyte
Conclusions

- Myelodysplastic syndromes are difficult to diagnose
- Clinical and diagnostic studies are imprecise
- Many of bone marrow failure entities overlap
- Cytogenetic and molecular testing is increasingly important