Myelodysplastic Syndromes

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Outline

• Introduction and classifications
  – Epidemiology
  – Presentation
  – Workup
• Diagnosis
• Prognosis
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Blood stem cell

Cortical bone
Spongy bone
Marrow

Blood Vessel
Classification of Human Cancers

Liquid Tumors; Hematologic Cancers
e.g.
Lymphoma
Leukemias
Multiple Myeloma
...

Solid Tumors; e.g.
Breast Cancer
Lung Cancer
Colorectal cancer
...

Lymphoid

Myeloid
Classification of Myeloid Cancers

AML

MDS

MPN-eos

MPN

2008 WHO classification of myeloid malignancies

MDS/MPN

CMML
JMML
aCML
MDS/MPN-U (e.g., RARS-T)

BCR-ABL

JAK2 V617F

CML
PV
ET
PMF

JAK2 Exon 12

MPL W515

CNL
CEL-NOS
SM
MPN-U

PDGFR rearranged

FGFR1 rearranged

KIT D816V
MDS Progression to Acute Myeloid Leukemia

Hematopoietic Stem Cell → Common Myeloid Progenitor → Megakaryocyte → Platelets

Common Myeloid Progenitor → Red Blood Cells → Erythroblast → Erythrocyte

Common Myeloid Progenitor → Myeloblast → Myeloid Cell Lineage

MDS Stem Cell → Cytogenetic, Genetic, and/or Epigenetic

Leukemic Stem Cell → 2nd Hit → Aberrant Growth Signals and Reduced Apoptosis

Progenitor → Myeloblast → Megakaryocyte → Platelets

Myeloblast → Monocyte → Macrophage

Myeloblast → Basophil → Eosinophil → Neutrophil

MDS is Cancer

A Syndrome…

A heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective hematopoiesis.
How myelodysplastic syndrome was first described to patients. Note that patients could select more than one answer.

- Bone marrow disorder: 80.2%
- Anemia: 56.4%
- Blood disorder: 31.6%
- Neutropenia: 19.0%
- Thrombocytopenia: 17.0%
- Syndrome: 15.1%
- Other: 7.5%
- Cancer: 7.3%
- Leukemia: 5.9%
- Hematologic malignancy: 3.6%
Myelodysplastic Syndromes

• Recognized for over 50 years, termed Preleukemia, Smoldering Leukemia, Oligoblastic Leukemia, and Refractory Anemia.

• Denotes a variable risk of progression to:…
  • BM failure
  • AML:
    – Severe cytopenia, increased blasts, or cytogenetic abnormalities correlate with poor outcomes not different from acute leukemia.
    – Lack of these features is associated with long survival.
The precise incidence of de novo MDS is not known. Believed to be underestimated.

2004 SEER data
- Estimated to be 3.3 (2-12.6) per 100,000
- >60,000 individuals in USA
- >10,000 new cases /year
- Overall relative 3-year survival was 45%.

The median age is ≥65 years, with a male predominance

Incidence increases with age

Epidemiology

Incidence per 100,000

AGE

<50 50-60 60-70 70-80 >80
Clinical Presentation and Diagnosis
Clinical Presentation and Diagnosis

• No specific associated symptoms or signs.

• Most diagnoses are made subsequent to abnormal routine laboratory testing showing quantitative changes of one or more blood elements.

Definitions:

ANEMIA: decreased Red Blood Cells /Hemoglobin

THROMBOCYTOPENIA: decreased Blood Platelets

NEUTROPENIA: decreased White Blood Cells (Neutrophils)
Clinical Features of MDS

Anemia is hallmark - challenging to treat, many will require RBC transfusions

PNH
AvN
Iron Overload
Anemia
AML Transformation
Hyperuricemia
Neutropenia - infections
Thrombocytopenia: bleeding
Immune Disorders
Clinical Presentation and Diagnosis

• Symptoms are related to the degree of anemia, less commonly due to thrombocytopenia, and neutropenia.

• Associated constitutional symptoms, or autoimmune deregulation are uncommon.
Clinical Presentation and Diagnosis

- Findings at time of diagnosis:
  - Anemia is almost uniformly present: 95-100%
  - Pancytopenia 50 %
  - Isolated neutropenia, thrombocytopenia, or monocytosis in the absence of anemia: Less than 5 %
Predisposing Factors

• Advanced age
• Mutagen exposure:
  – Chemotherapy
    • Alkylators
    • Topoisomerase II inhibitors
  – Radiation exposure
  – Hematopoietic cell transplantation
  – Environmental
    • Benzene
    • Tobacco use: (HR 1.68, 3.17)
• Other primary hematologic disorders:
  – Aplastic anemia
  – Paroxysmal nocturnal hemoglobinuria (PNH)
  – Myeloproliferative disorders
• Hereditary predisposition:
  – DNA repair defects
  – Congenital and genetic disorders
• Obesity (HR 1.15 and 2.18)
Diagnosis and Classification
Diagnosis and Classification

• Careful evaluation of the peripheral smear.

• Evaluation of the duration of abnormal blood counts and other potential causes

• Exclusion of confounding factory: nutritional deficiencies, co-morbidities, chronic infections or autoimmune disorders.
Diagnosis and Classification

- Diagnosis is confirmed by a BM biopsy and aspirate.
- Identify and quantify dysplastic features, and involved lineages.
- Assess marrow cellularity, fibrosis, and topography.
- Sample for cytogenetic studies.
- Molecular testing, mutation analysis, and DNA sequencing.
- Classification.
- Has prognostic relevance.
<table>
<thead>
<tr>
<th>Category</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monocytes (10^9/L)</td>
<td>Blast (%)</td>
</tr>
<tr>
<td>Refractory anemia (RA)</td>
<td>≤1</td>
<td>≤1%</td>
</tr>
<tr>
<td>RA with ring sideroblasts (RARS)</td>
<td>≤1</td>
<td>≤1%</td>
</tr>
<tr>
<td>RA with excess of blasts (RAEB)</td>
<td>≤1</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia (CMML)</td>
<td>&gt;1</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>RAEB “in transformation” (RAEB-t)</td>
<td>≤1</td>
<td>≥5%</td>
</tr>
<tr>
<td>Subtype</td>
<td>Blood</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD)°</td>
<td>Single or bicytopenia</td>
<td>Dysplasia in ≥ 10% of one cell line, &lt; 5% blasts</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia, no blasts</td>
<td>≥ 15% of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, &lt; 5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenia(s), &lt; 1 x 10^9/L monocytes</td>
<td>Dysplasia in ≥ 10% of cells in ≥ 2 hematopoietic lineages, ± 15% ring sideroblasts, &lt; 5% blasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenia(s), ≤ 2%-4% blasts, &lt; 1 x 10^9/L monocytes</td>
<td>Unilineage or multilineage dysplasia, No Auer rods, 5%-9% blasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenia(s), 5%-19% blasts, &lt; 1 x 10^9/L monocytes</td>
<td>Unilineage or multilineage dysplasia Auer rods, ± 10%-19% blasts</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, &lt; 5% blasts</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anemia, platelets normal or increased</td>
<td>Unilineage erythroid dysplasia, isolated del(5q), &lt; 5% blasts</td>
</tr>
<tr>
<td>MDS subtype</td>
<td>Abbreviation</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>MDS with single lineage dysplasia</td>
<td>MDS-SLD</td>
<td>1 dysplastic lineage and 1–2 cytopenias</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia</td>
<td>MDS-MLD</td>
<td>2–3 dysplastic lineages and 1–3 cytopenias</td>
</tr>
<tr>
<td>MDS with ring sideroblasts</td>
<td>MDS-RS</td>
<td>≥ 15% ring sideroblasts, or ≥ 5% ring sideroblasts if mutation of SF3B1 present</td>
</tr>
<tr>
<td>MDS with excess blasts</td>
<td>MDS-EB</td>
<td>5–9% BM blasts (MDS-EB-1) or 10–19% BM blasts (MDS-EB-2)</td>
</tr>
<tr>
<td>MDS unclassified</td>
<td>MDS-U</td>
<td>del(5q) cytogenetic abnormality alone or with 1 additional abnormality other than −7 or del(7q)</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
# Myelodysplastic/Myleoproliferative Neoplasms (MDS/MPN) WHO Classification

<table>
<thead>
<tr>
<th>Subtype</th>
</tr>
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<tbody>
<tr>
<td>Chronic myelomonocytic leukemia-1 (CMML-1)</td>
</tr>
<tr>
<td>CMML-2</td>
</tr>
<tr>
<td>Atypical chronic myeloid leukemia (CML), BCR-ABL1 negative</td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukemia (JMML)</td>
</tr>
<tr>
<td>MDS/MPN, unclassifiable ('Overlap syndrome')</td>
</tr>
</tbody>
</table>

![Diagram](image-url)
Prognosis
Prognosis

- International Prognostic Scoring System (IPSS) was developed by The International MDS Risk Analysis Workshop.

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
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<tr>
<td>Marrow blasts (%)</td>
<td>&lt;5</td>
<td>5–10</td>
<td>11–20</td>
<td>21–30</td>
<td></td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias†</td>
<td>0 or 1</td>
<td>2 or 3</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>IPSS Risk Group</th>
<th>Score</th>
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<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>High</td>
<td>2.5–3.5</td>
</tr>
</tbody>
</table>

*Good: normal, del(5q) only, del(20q) only, −Y only; Poor: very complex (>2) abnormalities, chromosome 7 abnormalities; Intermediate: other abnormalities.
†Cytopenias: hemoglobin <10 g/dL, neutrophil count < 1.8 × 10^9/L, platelet count < 100 × 10^9/L.
<table>
<thead>
<tr>
<th>Time in Years</th>
<th>Median OS</th>
<th>AML in 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>low risk</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Int-1</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>high risk</td>
<td>0.4</td>
<td>0.2</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Median OS</th>
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<tbody>
<tr>
<td>&lt; 60</td>
<td>11.8</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>4.8</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>3.9</td>
</tr>
</tbody>
</table>
## IPSS-Revised

<table>
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<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>
<td></td>
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</tbody>
</table>

### Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Score</th>
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<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>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>

### Prognostic Subgroups

- **Very good (4%*/3%*)**
  - -Y, del(11q)
- **Good (72%*/66%*)**
  - Normal, del(5q), del(12p), del(20q), double including del(5q)
- **Intermediate (13%*/19%*)**
  - del(7q), +8, +19, i(17q), any other single or double independent clones
- **Poor (4%*/5%*)**
  - -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities
- **Very poor (7%*/7%*)**
  - Complex: >3 abnormalities
Survival based on IPSS-R prognostic risk-based categories. n=7012.

AML evolution based on IPSS-R prognostic risk-based categories. n=6485.


<table>
<thead>
<tr>
<th>IPSS-R</th>
<th>n</th>
<th>Median OS</th>
<th>AML 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>1313</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>Low</td>
<td>2646</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1433</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>898</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>722</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Other Prognostic Models

- **WHO PROGNOSTIC SCORING SYSTEM (WPSS)**
- **MD ANDERSON CANCER CENTER MDS MODEL**
- **Individual risk factors:**
  - Increased age
  - Poor performance status, presence of comorbidities
  - Total WBC >20,000/microL, Eosinophilia (>350/microL) and basophilia (>250/microL)
  - Absolute lymphocyte count <1200/microL
  - Severity of anemia, Transfusion dependence
  - Refractory or severe (<30,000/microL) thrombocytopenia
  - CD34 positivity of bone marrow nucleated cells
  - Gene expression profiling
  - **Increased DNA methylation**
  - Following treatment failure with decitabine
  - Increased expression of the Wilms' tumor gene (WT1)
  - Increased serum beta-2 microglobulin concentration
  - **Mutations of the FLT3, EZH2, or ETV6 genes**, Absence of TET2 mutations
  - Presence of marrow fibrosis
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