Myelodysplastic Syndromes: Everyday Challenges and Pitfalls

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Henry Moon lecture
May 2007
Outline

• Definition
• Conceptual overview; pathophysiologic mechanisms
• Incidence, epidemiologic features
• Diagnostic tools and strategies
• Diagnostic challenges
• Practical approach/key tips
MDS: Definition

- Acquired clonal HP neoplasm, stem cell-derived
- Maturation of hematopoietic lineages intact, but inadequate overall cell production → cytopenias
- Blast count normal to increased (< 20%)
- Increased risk of leukemic transformation (loss of maturation)
MDS: Incidence

• Primarily disease of elderly; can occur at all ages
• 40 per one million adults
• Incidence increases with age: 15-50 per 100,000 in elderly patients (> 70 years)
• MDS in infants/children linked to either constitutional disorders or prior chemotherapy
MDS: Key Considerations

Clinical:

- Prolonged, unexplained cytopenia (usually symptomatic)
- Stable vs. progressive cytopenia(s)
- Search for causes, risk factors, exposures, medications
- Exclude collagen vascular disease, chronic viral infection
- ↑ in frequency of therapy-related MDS (30% MDS)
Neutropenia; assess qual/quant all lineages
MDS: Key Features

Blood:
- Cytopenias
- Variable dysplasia (assess all hematopoietic lineages)
- Variable blasts (low)

Bone Marrow:
- Hypercellular
- Dysplasia (one or more lineages); ringed sideroblasts, coarse Fe granules
- Variable blast % (often ↑ for patient age)
MYELOID NEOPLASMS

MATURATION FAILURE

AML

Blastic transformation

INTACT MATURATION

MDS

Blastic transformation

MDS/MPD

Blast phase

CMPD
# Myeloid Neoplasms

<table>
<thead>
<tr>
<th>Failed Hematopoiesis</th>
<th>Under-Production</th>
<th>Excess Cell Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myelogenous Leukemia and Blastic Transformations</td>
<td>Myelodysplasias</td>
<td>Myeloproliferative Disorders and MDS/MPD</td>
</tr>
</tbody>
</table>
# Usual Features of Myeloid Neoplasms (at diagnosis)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Bld Counts</th>
<th>BM Cellularity</th>
<th>% BM Blasts</th>
<th>Maturation Morphol</th>
<th>Spl/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMPD</td>
<td>↑↑</td>
<td>Nl - ↑↑↑</td>
<td>Normal</td>
<td>Present</td>
<td>Nl (megas)</td>
</tr>
<tr>
<td>MDS</td>
<td>↓↓</td>
<td>↑ (usu)</td>
<td>Nl – 19%</td>
<td>Present</td>
<td>Dyspl.</td>
</tr>
<tr>
<td>MDS/MPD</td>
<td>↑, ↓</td>
<td>↑↑</td>
<td>Nl – 19%</td>
<td>Present</td>
<td>Dyspl.</td>
</tr>
<tr>
<td>AML</td>
<td>↑, ↓</td>
<td>↓ - ↑↑ (usu)</td>
<td>≥ 20%</td>
<td>Minimal (usu)</td>
<td>Dyspl. (usu)</td>
</tr>
</tbody>
</table>
Comparison of blood features
Comparison of bone marrow features
Blood Findings Suggestive of MDS

- Single or multilineage cytopenias
- Left shift with myeloblasts (< 20%)
- Single/multilineage dysplasia
- Neutrophils with hypogranular cytoplasm and/or nuclear segmentation abnormalities
- Erythrocyte dysplasia with nucleated forms
- Enlarged, hypogranular platelets
Normal and abnormal neutrophils
MDS: pseudo Pelger-Hüet dysplasia
BM Findings Suggestive of MDS

- Hypercellularity
- Increased blasts (< 20%); clustered blasts
- Single/multilineage dysplasia
- Abnormal localization of myeloblasts and erythroid elements
- Increased, dysplastic, clustered megakaryocytes
- Prominent karyorrhexis (apoptosis)
- Ringed sideroblasts, coarse Fe granules in erythroid cells
MDS: increased megas, cellularity
MDS: erythroid dysplasia
Erythroid dysplasia
Platelet/mega dysplasia
Comparison of CD34
Pathophysiologic Mechanisms of MDS

• Multistep pathogenesis
• Acquired stem cell abnormality resulting in clonal hematopoiesis
• Stem cell and BM microenvironmental defects (complex interplay)
• Increased BM apoptosis (bld/BM paradox)
• Acquisition of clonal abnormalities linked to disease progression and/or transformation
Conventional Karyotype/FISH

- Normal conventional cytogenetics in > 40% of 1° MDS; abnormal karyotype in > 95% T-MDS
- Frequency of cytogenetic abnormalities linked to WHO subtype (lowest in RARS; highest in RCMD)
- Whole or partial deletions of chromosomes 5, 7, 20, 8
- Translocations very uncommon
## Cytogenetic Abnormalities in MDS

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td><strong>de novo</strong> MDS</td>
<td></td>
</tr>
<tr>
<td>-5/del(5q)</td>
<td>10-20%</td>
</tr>
<tr>
<td>+8</td>
<td>10%</td>
</tr>
<tr>
<td>-7/del(7q)</td>
<td>5-10%</td>
</tr>
<tr>
<td>17p-</td>
<td>7%</td>
</tr>
<tr>
<td>del(20q)</td>
<td>5%</td>
</tr>
<tr>
<td>complex abnls</td>
<td>10-20%</td>
</tr>
<tr>
<td>translocations</td>
<td>rare</td>
</tr>
<tr>
<td><strong>Therapy-related</strong></td>
<td></td>
</tr>
<tr>
<td>-5/del(5q) or -7/del(7q)</td>
<td>90%</td>
</tr>
<tr>
<td>complex abnls</td>
<td>90%</td>
</tr>
<tr>
<td>Translocation</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>
Conventional Cytogenetics

46,XX,del(5)(q31q33)[19]/46,XX[1]
Myeloid Malignancy w/ Complex Cytogenetic Abnormalities
Cytogenetics Risk (IPSS)

**Good:** Normal, del(5q) sole, del(20q) sole, -Y

**Intermediate:** Other

**Poor:** -7, del(7q), complex abnormalities
MDS: Diagnostic Tools and Strategies

- Serial CBC data
- Blood smear for morphologic review
- Bone marrow aspirate, biopsy, iron stain
- IHC of bone marrow core biopsy
- Flow cytometry of bone marrow aspirate
- Conventional cytogenetics; selected FISH
- IPSS (International Prognostic Scoring System)
# IPSS (International Prognostic Scoring System)

*Risk score is determined by % BM blasts, cytogenetics, degree of cytopenias*

<table>
<thead>
<tr>
<th>Score Value</th>
<th>Prognostic variable</th>
<th>% BM blasts</th>
<th>Karyotype</th>
<th>Cytopenias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>&lt; 5</td>
<td>Good</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>5-10</td>
<td>Intermediate</td>
<td>2/3</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td></td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## IPSS (International Prognostic Scoring System)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>vs. Median Survival (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Int-1</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.5 – 2.0</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 2.5</td>
</tr>
</tbody>
</table>
Exemplary Case

Refractory Cytopenia w/ Multilineage Dysplasia

- 65 y.o. female
- CBC: pancytopenia
- BM Asp: Blasts 5%, dx:RCMD
- CC: del(5q31), del(9q), del(20q)
- IPSS: Poor risk
## WHO Classification of MDS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood Findings</th>
<th>BM Findings</th>
<th>Freq. of Cytog. Abnls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>• Anemia</td>
<td>• Erythroid dysplasia only</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>• No or rare blasts</td>
<td>• &lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt; 15% ringed sideroblasts</td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>• Anemia</td>
<td>• Erythroid dysplasia only</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>• No or rare blasts</td>
<td>• &lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 15% ringed sideroblasts</td>
<td></td>
</tr>
<tr>
<td>RCMD</td>
<td>• Bi- or pancytopenia</td>
<td>Dysplasia in 10% cells of ≥ 2 myeloid lineages</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>• No or rare blasts</td>
<td>• &lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td>RCMDv</td>
<td>• Bi- or pancytopenia</td>
<td>Dysplasia in 10% cells of ≥ 2 myeloid lineages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No or rare blasts</td>
<td>• &lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 15% ringed sideroblasts</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Blood Findings</td>
<td>BM Findings</td>
<td>Freq. of Cytog. Abnls*</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>RAEB-1</strong></td>
<td>• Cytopenias</td>
<td>• Unilineage or multilineage dysplasia</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>• &lt; 5% blasts</td>
<td>• 5 – 9% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No Auer rods</td>
<td></td>
</tr>
<tr>
<td><strong>RAEB-2</strong></td>
<td>• Cytopenias</td>
<td>• Unilineage or multilineage dysplasia</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>• 5-19% blasts</td>
<td>• 10 – 19% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Auer rods +/-</td>
<td>• Auer rods +/-</td>
<td></td>
</tr>
<tr>
<td><strong>5q- syndrome</strong></td>
<td>• Anemia</td>
<td>• NI in ↑ megas w/ hypolobated nuclei</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>• Usu. nl or ↑ platelets</td>
<td>• &lt; 5% blasts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &lt; 5% blasts</td>
<td>• del(5q) only cytog. abnormality</td>
<td></td>
</tr>
<tr>
<td><strong>Myelodysplasia, unclassified</strong></td>
<td></td>
<td></td>
<td>*No cytog. feature specific for MDS</td>
</tr>
</tbody>
</table>
Exemplary Case

74-year-old female with fatigue

**CBC:**  WBC 3.8  (ANC 2.9)
RBC 2.9     MCV 104 fl
Hgb 10.1    RDW 14%
Hct 30%     Plt 411
Elderly female with macrocytic anemia
Elderly female with macrocytic anemia
Elderly female with macrocytic anemia
Elderly female with macrocytic anemia
Elderly female with macrocytic anemia

Prussian blue
Elderly female with macrocytic anemia
BM Differential:
2% blasts
45% erythroid
60% cellularity
↑ abnormal megakaryocytes

Cytogenetics: 47,XX,+19[17],46,XX[3]

IPSS: Int-1
Diagnosis?

RARS

vs.

RCMDv
MDS Diagnostic Challenges

Low grade MDS vs. benign:

*Diagnosis of exclusion*

- Normal karyotype
- Stable CBC
- Borderline dysplasia

Trisomy 6
MDS Diagnostic Challenges

Distinction between true dysplasia vs. “abnormal” morphology

- G-CSF or EPO-driven BM
- Medication-related dyspoiesis
- Significance of low frequency, subtle findings

Familial P-H/med.
MDS Diagnostic Challenges

Other causes of dysplasia in blood, BM

- Nutritional deficiency
- Drug exposures
- Underlying chronic infections
- Inflammatory, autoimmune disorders
- Dietary supplements (zinc)
- Toxins, poisons

Copper deficiency
Megaloblastic anemia, normal MCV
HIV-related dysplasia
MDS Diagnostic Challenges

MDS vs. low blast count AML

• Most frequently issue with t(8;21), inv(16), t(15;17) AMLs
• Morphologic “clues” to distinct AML subtypes
• Careful delineation of blasts, blast equivalents
• 20% blasts (blast equivalent) threshold

15% blasts, t(8;21)
Tips to Assess Dysplasia

- Focus on specific dysplastic features such as hypogranular cytoplasm of neutrophils and neutrophil nuclear hypo- or hypersegmentation.

- Be aware that many non-neoplastic conditions are associated with anisopoikilocytosis of RBC’s and nuclear aberrations of erythroid elements in BM.
Tips to Assess Dysplasia

• Assess proportion of cells within a given lineage with abnormal morphology; rare unusual cells are of unlikely significance.

• Assess for multilineage dysplasia

• Assess % of myeloblasts/blast equivalents. ↑ blasts in conjunction w/ significant dysplasia is strong predictor of MDS.
MDS: Practical Approach/Key Tips

- Consider clinical and hematologic “data”, especially sequential CBCs
- Be wary of isolated, low frequency RBC, erythroid lineage abnormalities (lack specificity)
- Technically excellent slide preparations essential
- Evaluate all lineages for MDS features or clues to prototypic low blast count AML subtypes
MDS: Practical Approach/Key Tips

• Careful blast enumeration (do not use CD34 by flow as surrogate for blast %)

• Assess bone marrow architecture by immunohistochemistry

• Full karyotyping recommended (targeted FISH may be useful)