Myelodysplasia
New Tools
New Tips
New Issues

Kathryn Foucar
Distinguished Professor Emerita of Pathology, UNM HSC
kfoucar@salud.unm.edu

ISLH Educational workshop
May 2017
Objectives

• Review the role of pathologists and laboratorians in MDS diagnosis and prognosis
• Present criteria and challenges for dysplasia assessment
• Review WHO 2016 criteria for MDS diagnosis and IPSS-Revised scoring
• Present morphologic, genetic and molecular traps in MDS
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)
Myelodysplasia

- Ineffective HP results in cytopenias despite hypercellular BM
- Hallmark of cytopenias with dysplasia (≥ 10%)
- Variable % blasts in blood and BM
- Dysplasia may involve 1, 2, or 3 HP lineages
- 7 WHO 2008 subtypes/same for 2016
Myelodysplasia

- Major impact of WHO subtype, karyotype and IPSS-R on prognosis
- Low grade MDS: Diagnosis of exclusion
- High grade MDS: Biologic continuum with AML (esp AML with MDS-related changes)
- Low blast count AML: t(8;21), inv(16)
MDS: Incidence

- Primarily disease of elderly; can occur at all ages
- 40 cases 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 (germline) disorders or prior chemotherapy
MDS: Key Considerations

Clinical:

- Prolonged, unexplained cytopenia (variably 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)
Low-grade MDS vs. Benign Disorder

- Clinical correlation; search for cause of cytopenia
- Medication history/homeopathic remedies
- Appreciate more newly recognized causes of prolonged cytopenias (e.g.-zinc induced copper deficiency)
- Sequential CBC data; progression of cytopenia or development of new cytopenia favors MDS
- Systematic assessment of blood/BM
- Cytogenetics a must
2 year old with new onset pancytopenia

Copper deficiency; on TPN
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
MDS: Key Features

Blood:

- Cytopenias
- Variable dysplasia (assess all hematopoietic lineages)
- Variable blasts (usually low) ($\leq 20\%$)

Bone Marrow:

- Hypercellular
- Dysplasia ($\geq 10\%$) (one or more lineages); ringed sideroblasts, coarse Fe granules
- Variable blast % (often $\uparrow$ for patient age) ($\leq 20\%$)
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
Trilineage dysplasia
Normal and abnormal neutrophils
MDS: pseudo Pelger-Hüet dysplasia
BM Findings Suggestive of MDS

- Hypercellularity
- Increased blasts (< 20%); clustered blasts
- Single/multilineage dysplasia (≥ 10% threshold)
- Abnormal localization of myeloblasts and erythroid lineage cells
- Increased, dysplastic, clustered megakaryocytes
- Prominent karyorrhexis (apoptosis)
- Ringed sideroblasts, coarse Fe granules in erythroid cells
MDS: increased megas, cellularity
MDS: erythroid dysplasia
Dysplasia in Each Lineage

Percent dysplastic cells critical
Megakaryocyte Assessment in MDS

Increased, hypolobated megakaryocytes
Systematic Approach: Dysplasia

• What morphologic features constitute dysplasia?
• Dysplastic cells must exceed 10% in a lineage
• Dysplasia assessment very challenging
  – lack of consensus at 10% threshold
  – better consensus at 40% threshold, especially for megakaryocytes
• Dysplasia assessment based on blood and BM aspirate smears for erythroid and granulocytic lineages
• Megakaryocyte dysplasia based on evaluation of at least 30 megakaryocytes on core biopsy sections
Dysplasia Caveats

• Many benign causes of RBC pathology in blood and bone marrow

• Excellent stain quality **essential** to assess neutrophils, identify blasts

• Adequacy of BMA and Bx key

• Know key MDS mimics
MDS-2016

• All new names; all criteria retained

• SF3B1 mutations in cases with ring sideroblasts (lower % criteria)

• AEL (myeloid/erythroid) cases will become MDS-EB

(EB = Excess blasts)
2016 MDS Terminology

• MDS with single lineage dysplasia (SLD)
• MDS with ring sideroblasts (RS) : single vs multilineage dysplasia
• MDS with isolated del 5q
• MDS with multilineage dysplasia (MLD)
• MDS with excess blasts 1 (MDS-EB1)
• MDS with excess blasts 2 (MDS-EB2)
• MDS, unclassifiable
Additional WHO 2016 MDS Tips 1

• Molecular testing for \textit{SF3B1} mutations useful in cases with ring sideroblasts (MDS with RS) (threshold lowered to $\geq 5\%$ ring sideroblasts if positive)

• Molecular testing for \textit{TP53} mutations useful for prognosis
• One additional cytogenetic abnormality allowed for MDS with “isolated” del 5q
  – **Cannot** involve chromosome 7
  – **Cannot** by MDS-related abnormality
• Cases formerly fulfilling criteria for AEL, myeloid/erythroid will often become MDS-EB
  – Alert clinician to monitor carefully for progression to overt AML
  – Test for *NPM1* and *MLL (KMT2A)* mutations; if positive suggest **evolving** AML
MDS: Report and Studies Needed

- Must still count morphologic blast % in blood and BM and include actual % in report
- Provide % dysplasia (≥ 10%) (any unique features)
- Flow cytometry “ok” as ancillary tool, but not required
- Flow blast % should not replace morphologic %
- Cytogenetics required on all cases (del 5q, other)
- Molecular testing has utility (e.g. SF3B1 (if rings), NPM1/KMT2A (if approaches AML), TP53 (prognosis)
Molecular Caveats

• Mutations linked to MDS/AML detected in blood of healthy individuals; frequency linked to age

• CHIP: Clonal Hematopoiesis of Indeterminant Potential

• Consequently mutations detected by NGS cannot be used to diagnose MDS in cases lacking dysplasia or cytogenetic abnormalities
Prognostication in MDS

• Essential; IPSS-R score predicts outcome

• Lab/pathology provide all data used for prognosis determination

• Our pathology reports must provide all necessary data for IPSS-R score
# Myelodysplasia Blast Percentages

<table>
<thead>
<tr>
<th>Proposed WHO 2016 (no change from 2008)</th>
<th>IPSS-R* Risk factor score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood: &lt;1%, 1%, &lt;2%, &lt;5%, 5-19%</td>
<td>No blood blast % required</td>
</tr>
<tr>
<td>Bone Marrow: &lt;5%, 5-9%, 10-19%</td>
<td>≤2%, &gt;2-%&lt;5%, 5-10%, &gt;10%</td>
</tr>
</tbody>
</table>


Must include blast % in **Blood** and **Bone Marrow** in report.
## 2012 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>--</td>
<td>Good</td>
<td>--</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
</tr>
<tr>
<td>BM blast, %</td>
<td>≤ 2%</td>
<td>--</td>
<td>&gt; 2-5%</td>
<td>--</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td>--</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10</td>
<td>--</td>
<td>8 - &lt;10</td>
<td>&lt; 8</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>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
# IPSS-R Cytogenetic Risk Groups

<table>
<thead>
<tr>
<th>Cytogenetic prognostic subgroups</th>
<th>Cytogenetic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>-Y, del(11q)</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Complex: &gt; 3 abnormalities</td>
</tr>
</tbody>
</table>

## Revised International Prognostic Scoring System (IPSS-R)

<table>
<thead>
<tr>
<th>IPSS-R Risk Category</th>
<th>Overall Score</th>
<th>Median Survival (Y) No Rx</th>
<th>25% AML Progression No Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY LOW</td>
<td>≤ 1.5</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>LOW</td>
<td>&gt; 1.5 - ≤ 3.0</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>INT</td>
<td>&gt; 3.0 - ≤ 4.5</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>HIGH</td>
<td>&gt; 4.5- ≤ 6.0</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>VERY HIGH</td>
<td>&gt; 6.0</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Exemplary Case

- **Patient:** 54-yr-old male with malaise for one month and pancytopenia

- **CBC:** WBC 2.9, RBC 1.7, H/H 6.1/18%, Plt 77
Blood

Cytopenias, dysplasia
Blood

Cytopenias; blasts (7%)
Bone Marrow Aspirate

Dyserythropoiesis; 80% erythroid cells
Left-shift; 5% myeloblasts
Immaturity, dysplasia; erythroid predominance
BM Bx

CD34 about 5%
Diagnosis: MDS-EB2

CC: Complex abnormalities >3

IPSS-R score: 8.0 (very high risk)

Tip: Blast percent based on all cells (except lymphoid neoplasm) (WHO 2016)

Based on WHO 2008 would be diagnosed as AEL
MDS: Grey Zones

- **ICUS**: idiopathic cytopenia of uncertain significance
- **CCUS**: clonal cytogenetic abnormality of uncertain significance
- **CHIP**: clonal hematopoiesis of indeterminant potential
MDS Diagnostic Challenges

Clonal cytogenetic abnormality of uncertain significance (CCUS)

• Normal BM blast %
• Stable CBC
• Borderline dysplasia (< 10%)

Trisomy 6 or Trisomy 15
MDS Diagnostic Challenges

Other causes of cytopenias with 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
ICUS†

• Persistent cytopenia
• No cause determined
• Case does not meet MDS criteria (dysplasia and/or blast thresholds); normal cytogenetics
• About one third of anemias in elderly “unexplained”

‡ NGS may be abnormal
MDS Diagnostic Challenges

MDS vs. low blast count AML

- Most frequently issue with t(8;21), inv(16), t(15;17) AMLs
- Note that t(8;21), inv(16) and t(15;17) AML-defining regardless of blast %
- Morphologic “clues” to distinct AML subtypes
- Careful delineation of blasts, blast equivalents
- 20% blasts (blast equivalent) threshold for other AML’s

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 lineage cells 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
- Cytogenetics a must if BME performed
MDS: Reporting

• Integrate morphology, CBC, flow (if performed) and cytogenetics (team effort)
• Integrate molecular if performed and provide prognostic significance
• Provide all pathology information needed for IPSS-R (provide score if possible)
• WHO category with discussion of any unique features and discussion of significance of cytogenetic findings
Myelodysplasia

• Major impact of WHO subtype, karyotype and IPSS-R on prognosis

• Low grade MDS: Diagnosis of exclusion

• Grey Zone: ICUS, CCUS, CHIP

• High grade MDS: Biologic continuum with AML (esp. AML with MDS-related changes)

• Low blast count AML: t(8;21), inv(16)