MYELODYSPLASTIC SYNDROMES

Definition
- Unexplained cytopenia(s)
- Ineffective hematopoiesis
- Dysplasia
- High risk of AML transformation

Etiology
- De novo
- Secondary MDS (10 years earlier than primary)
  - Therapy-related
  - Chemotherapy (alkylating agents, topoisomerase-II inhibitors)
  - Ionizing radiation
  - Exposure to toxins: benzene
  - Familial predisposition
  - Immunosuppression
  - Infections: HIV

No relevant COIs to disclose
IWG-MDS Minimum Diagnostic criteria

• **Cytopenia(s)**
  - Unexplained
  - Exclude other potential reasons for cytopenia/dysplasia
  - Stable/persistent (≥6 months)
  - 2 months in the presence of bilineage dysplasia or specific karyotype

• **MDS-related decisive criteria (≥1 of 3)**
  - Dysplasia(s)
    - At least 1 cell lineage
  - BM blasts 5-19%
  - MDS-defining cytogenetic abnormality

References: 2016 WHO; NCCN 2017

IWG Minimum Diagnostic criteria

• **MDS co-criteria (helpful)**
  - Aberrant immunophenotype by flow cytometry
  - Abnormal bone marrow histology and immunohistochemistry
  - Abnormal CD34 antigen expression
  - Fibrosis
  - Dysplastic megakaryocytes
  - Atypical localization of immature progenitors
  - Molecular markers of clonality

References: 2016 WHO; NCCN 2017

2016 WHO criteria for diagnosis of MDS

1. **Cytopenia(s)**
2. **Dysplasia(s)**
   - At least 1 cell lineage
3. **MDS-defining cytogenetic abnormality**

References: 2016 WHO; NCCN 2017

1. **Cytopenia(s)**
   - Original IPSS (prognostication) cut-off values
     - Hemoglobin <10 g/dL
     - Absolute neutrophilic count < 1.8x10^9/L
     - Platelets <100x10^9/L
   - Often incidental during routine lab work

References: 2016 WHO; NCCN 2017
Suggestions

- Standard hematologic values more appropriate to define cytopenic cut points for MDS diagnosis
- Diagnosis possible with milder cytopenias
  - if other definitive diagnostic criteria present
- Use individual laboratory reference ranges
- Account for ethnic variation

2016 WHO criteria for diagnosis of MDS

2. Dysplasia

- At least 1 cell lineage(s)
- At least 10% of cells of any lineage
- No distinction between different morphologies

References: 2016 WHO; NCCN 2017
### Erythroid lineage

<table>
<thead>
<tr>
<th>Morphological abnormalities</th>
<th>Cutoff values</th>
<th>Variable weighted score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblastoid changes</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
<tr>
<td>Bi or multinucularity</td>
<td>&gt; 3%</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear lobulation or irregular contours</td>
<td>&gt; 3%</td>
<td>1</td>
</tr>
<tr>
<td>Pyknosis</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
<tr>
<td>Cytoplasmic fraying</td>
<td>≥ 7%</td>
<td>1</td>
</tr>
<tr>
<td>Ring sideroblasts</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
<tr>
<td>Ferritin sideroblasts</td>
<td>≥ 30%</td>
<td>1</td>
</tr>
</tbody>
</table>

### Granulocytic lineage

<table>
<thead>
<tr>
<th>Morphological abnormalities</th>
<th>Cutoff values</th>
<th>Variable weighted score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloblasts</td>
<td>&gt; 3%</td>
<td>1</td>
</tr>
<tr>
<td>Auer rods</td>
<td>&gt; 5%</td>
<td>3</td>
</tr>
<tr>
<td>Auer rods</td>
<td>≥ 1%</td>
<td>3</td>
</tr>
<tr>
<td>Pseudo Pelger–Hüet anomaly</td>
<td>&gt; 3%</td>
<td>1</td>
</tr>
<tr>
<td>Hypolobulated nuclei</td>
<td>&gt; 3%</td>
<td>1</td>
</tr>
<tr>
<td>Hypolobulated nuclei</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
<tr>
<td>Hypogranulated cytoplasm</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
<tr>
<td>Hypogranulated cytoplasm</td>
<td>&gt; 3%</td>
<td>1</td>
</tr>
<tr>
<td>Hypogranulated cytoplasm</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
</tbody>
</table>

### Megakaryocytic lineage

<table>
<thead>
<tr>
<th>Morphological abnormalities</th>
<th>Cutoff values</th>
<th>Variable weighted score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromegakaryocytes</td>
<td>&gt; 5%</td>
<td>3</td>
</tr>
<tr>
<td>Small binucleated megakaryocytes</td>
<td>&gt; 5%</td>
<td>1</td>
</tr>
<tr>
<td>Megakaryocytes with multiple separated nuclei</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
<tr>
<td>Hypolobated or monolobar megakaryocytes</td>
<td>&gt; 5%</td>
<td>2</td>
</tr>
</tbody>
</table>
- Standardization
- Not practical for routine work-up
- Difficult cases with ambiguous findings
- Minimum score of 3
- At least 10% of cells
- Certain abnormalities have “more weight”

Morphologic dysplasia is NOT specific

Non-clonal conditions show dysplasia
- Nutritional deficiencies:
  - Folate
  - Vitamin B12
  - Copper (Zinc induced)
- Medications
  - Sulfa drugs (PPH changes)
  - Chemotherapy
  - Growth factors
- Toxins
  - Heavy metals (arsenic), alcohol
- Viral infections
  - HIV, EBV, CMV, hepatitis B, parvovirus B19
- Autoimmune diseases
  - Lupus etc…
- Congenital hematologic disorders
  - Congenital dyserythropoietic anemia
- Familial predisposing conditions
  - RUNX1 mutation
  - Ankyrin mutation

Recommended immunohistochemical stains
1. CD34
   - Hemodilute smears
   - Hypocellular MDS/ hypoplastic AML/ Aplastic anemia
   - Multifocal accumulation of precursors
   - Angiogenesis
2. CD117
3. CD61/CD42/CD62/CD31/Factor 8
4. Tryptase
5. CD20, CD3, CD68, Lysozyme, cytokeratin
6. Fibrosis:
   1. Reticulin (Gomori’s silver impregnation)
   2. Trichrome

Ring sideroblast (type 3)

- 5 or more granules
- Perinuclear position
- Surrounding the nucleus or encompassing at least 1/3rd of the nuclear circumference

Mufti et al. Haematologica 2008; 93(11)
2016 WHO criteria for diagnosis of MDS

1. Cytopenia(s)
   - Hemoglobin <10 g/dL
   - ANC <1.5
   - Platelets <100 k
2. Dysplasia(s)
   - At least 1 cell lineage
3. MDS-defining cytogenetic abnormality

Reference: 2016 WHO

MDS-related cytogenetic abnormalities

- Patients with unexplained cytopenia(s) without dysplasia
- Presumptive evidence of MDS

- Y, trisomy 8 and del(20q) not disease defining

Essential component of MDS work-up

- Diagnostic
  - Identification of a malignant clone
  - ~50% de novo MDS; ~90% t-MDS
- Biological distinct entity: isolated del(5q)
- Prognostic stratification
- Basis for Rx selection
- Clues for molecular pathogenesis of MDS

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- Diagnostic
  - Identification of a malignant clone
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- Prognostic stratification & basis for Rx selection
- Clues for molecular pathogenesis of MDS

Cytogenetic Scoring System in MDS

- Very good
  - n=80 (2.9%)
  - Single: del(1q)
- Good
  - n=1844 (65.9%)
  - Single: del(1q)
- Intermediate
  - n=578 (20.7%)
  - Single: +8
  - Double: del(5q)
- Poor
  - n=101 (3.8%)
  - Single: +8
  - Complex: +3 abnormalities
- Very Poor
  - n=196 (7.0%)
  - Complex: +3 abnormalities

FISH in MDS

- FISH abnormal in only 2.7% of 222 cases with adequate cytogenetic studies

### Table 11

<table>
<thead>
<tr>
<th>Metaphase Cytogenetics</th>
<th>FISH Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (20 metaphase cells)</td>
<td>6/222 (2.7)</td>
</tr>
<tr>
<td>Suboptimal growth (&lt;20 metaphase cells)</td>
<td>6/43 (14)</td>
</tr>
<tr>
<td>No growth</td>
<td>10/54 (19)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>72/114 (63.2)</td>
</tr>
</tbody>
</table>

FISH, fluorescence in situ hybridization.

* Data are given as number/total (percentage).
Essential component of MDS work-up

- Diagnostic
  - Identification of a malignant clone
  - ~50% de novo MDS; ~90% t-MDS
- Biological distinct entity: isolated del(5q)
- Prognostic stratification & basis for Rx selection
- Clues for molecular pathogenesis of MDS

Genomic landscape of MDS

Somatic gene mutations

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribosomal proteins</td>
<td>RPS14</td>
</tr>
<tr>
<td>Epigenetic regulators</td>
<td>TET2, ASXL1</td>
</tr>
<tr>
<td>Splicing factors</td>
<td>SF3B1, SRSF2, U2AF1</td>
</tr>
<tr>
<td>Transcription factors</td>
<td>RUNX1, ETV6</td>
</tr>
<tr>
<td>Tyrosine kinase signaling</td>
<td>RAS</td>
</tr>
<tr>
<td>Tumor suppressor</td>
<td>TP53</td>
</tr>
</tbody>
</table>

**SF3B1 mutations in MDS**

- SF3B1 mutations in 20% MDS
- High frequency among patients with ring sideroblasts (65%)

Papaemmanuil, et al. NEJM 2011

MDS-RS with wild-type SF3B1 segregated with other MDS subtypes

- SF3B1 mutation
- MDS NOS
- MD-associated mutations


SF3B1 mutated MDS patients have better survival and lower risk of disease progression compared with SF3B1-unmutated cases

2016 WHO sub-classification

<table>
<thead>
<tr>
<th>2016 WHO Sub-classification</th>
<th>Dysplastic</th>
<th>Cytopenias</th>
<th>Ring sideroblasts%</th>
<th>PB blasts</th>
<th>BM blasts</th>
<th>Auer Rods</th>
<th>Karyotype [CC]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-SLD</td>
<td>1</td>
<td>1 or 2</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>any except &quot;isolated del(5q)&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-MLD</td>
<td>2 or 3</td>
<td>1-3</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>any except &quot;isolated del(5q)&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-RS-SLD</td>
<td>1</td>
<td>1 or 2</td>
<td>≥5%</td>
<td>&lt;1%</td>
<td>any except &quot;isolated del(5q)&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-RS-MLD</td>
<td>2 or 3</td>
<td>1-3</td>
<td>≥5%</td>
<td>&lt;1%</td>
<td>any except &quot;isolated del(5q)&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS with iso del(5q)</td>
<td>1-3</td>
<td>1-2</td>
<td>Any</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>Sole del(5q) or with 1 abnormality except -7 or del(7q)</td>
<td></td>
</tr>
<tr>
<td>MDS-EB-1</td>
<td>0-3</td>
<td>1-3</td>
<td>Any</td>
<td>2-4%</td>
<td>5-9%</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>MDS-EB-2</td>
<td>0-3</td>
<td>1-3</td>
<td>Any</td>
<td>5-19%</td>
<td>10-19%</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>MDS-3</td>
<td>1-3</td>
<td>1-3</td>
<td>Any</td>
<td>1%</td>
<td>&lt;5%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MDS-4</td>
<td>1</td>
<td>3</td>
<td>Any</td>
<td>1%</td>
<td>&lt;5%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MDS-5</td>
<td>0</td>
<td>1-3</td>
<td>&lt;15%</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>MDS-defining abnormality</td>
<td></td>
</tr>
</tbody>
</table>

2016 WHO sub-classification is prognostic

- MDS with ring sideroblasts
  - <5% BM blasts
  - Absent isolated del(5q)
  - ≥ 5% RS with SF3B1 mutation
  - ≥ 15% RS without SF3B1 mutation
  - < 5% RS with SF3B1 mutation
  - MDS-RS-SLD
  - MDS-RS-MLD

- MDS with isolated del(5q)
  - Allow 1 additional cytogenetic abnormality except monosomy 7 or del(7q)
  - Exclude >5% blasts

Mallo et al. Leukemia (2011) 25, 110–120
**MDS with isolated del(5q)**
- Recommend testing for TP53 mutation or p53 IHC
- Identify patients with poor response to lenalidomide

![Graph showing probability of AML from time (years) by TP53 mutation and p53++


**MDS-unclassifiable**
1. MDS-SLD with pancytopenia (<IPSS recommendation)
2. MDS with isolated del(5q) with pancytopenia (<IPSS recommendation)
3. 1% PB blasts (2 separate occasions) + <5% BM blasts
4. Normal morphology with MDS-defining cytogenetic abnormality

**MDS with erythroid predominance**
- 2008 WHO: >20% of non-erythroid lineage if >50% erythroid precursors
- Small changes in blast number between MDS and AEL
- Questionable benefit in AEL from intensive chemotherapy
- Blast% as a total of all nucleated cells (MDS-EB)
- Pure erythroid leukemia remains in AML

![Graph showing impact on survival and AML evolution for IWG-PM patients marrow blast subgroups]

Peter L. Greenberg et al. Blood 2012;120:2454-2465
©2012 by American Society of Hematology
**IPSS-R**

<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% – &lt; 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>

**Median (years)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Very Low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>≤ 1.5</td>
<td>&gt; 1.5 – 3.0</td>
<td>&gt; 3 – 4.5</td>
<td>&gt; 4.5 – 6.0</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>AML Transf</td>
<td>NR</td>
<td>NR</td>
<td>15.7</td>
<td>4.8</td>
<td>2.6</td>
</tr>
<tr>
<td>25% AML Transf</td>
<td>NR</td>
<td>10.8</td>
<td>3.2</td>
<td>1.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Gene mutations influence outcome**

- Mutation absent (N=302)
- Mutation present (N=137)

P<0.001

**Single gene assays to NGS**

- Evidence of clonality in appropriate clinical context
- Define homogeneous MDS subtypes
- Predictors of outcome
- Targeted therapy
- Follow-up

- Multiple genes
- Semi-quantitative
- Better detection ability for low-level mutations
- Clonal evolution


Evidence of clonality in appropriate clinical context

Define homogeneous MDS subtypes

Predictors of outcome

Targeted therapy

Follow-up
**SPECIAL CONSIDERATIONS**

**CHIP as a precursor state for hematological neoplasms**

- Steensma et al. Blood 2015;126:9-16

**Genetics of MDS: from clonal hematopoiesis to secondary AML**

- **Hypocellular MDS vs. Aplastic Anemia**
  - Presence of PB blasts
  - Increased (>1-19% BM blasts)
    - ALIP positive [at least 3 aggregates (>5 myeloid precursors) or clusters (3-5 myeloid precursors) per section]
    - Increased CD34 positive cells
  - Easily recognizable MKs
  - Dysplasia
    - >10% hypogranular neutrophils or pseudo-Pelger neutrophils
    - Dysplasia of granulocytes or megakaryocytes
    - Moderate to severe erythroid dysplasia
    - Ring sideroblasts
  - Cytogenetic abnormalities [not trisomy 8, UPD 6p, del(13q)]

Other inherited bone marrow failures

- Fanconi anemia
- Dyskeratosis Congenita
- Shwachman-Diamond syndrome
- Diamond Blackfan anemia
- Severe Congenital Neutropenia
- Congenital amegakaryocytic thrombocytopenia

Germline predisposition syndromes

- Can present de novo and in adulthood
- Dysmegakaryopoiesis frequent!
- Confirm by testing skin fibroblasts
- Implications for family members
Diagnosis of MDS in germline predisposition syndromes

Table 3. Proposed criteria for diagnosing myelodysplastic syndrome in individuals with familial platelet disorder with propensity for myeloid malignancy and germline RUNX1 mutations.

**Major criteria**
1. Identification of germline RUNX1 mutation
2. Cytopenia in a1 hematopoietic lineage, other than thrombocytopenia
3. Exclusion of non-myelocytic causes of cytopenia
4. Bone marrow and peripheral blood blasts <20%

**Minor criteria**
A. Morphologic features of myelodysplasia in all hematopoietic lineages
B. Acquired clonal cytogenetic or molecular genetic abnormality


MDS with fibrosis


Spectrum of Indolent Myeloid Hematopoietic Disorders

<table>
<thead>
<tr>
<th>Feature</th>
<th>ICUS</th>
<th>IDUS</th>
<th>CHIP</th>
<th>CCUS</th>
<th>MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic mutation</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Clonal karyotypic abnormality</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Marrow dysplasia</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

NCCN 2017

- Blasts 20-30%
- If ≥2 months → MDS or AML
- MDS-EB-T
  - Excess blasts in transformation

Multimodal approach to BM work-up in suspected hematological malignancy

1. Clinical information
2. Blood counts and chemistry
3. Peripheral Blood Smear
4. Bone marrow

Aspirate
- Aspirate smear
- Wright Giemsa

Heparin anticoagulant (2 mL in 0.5 mL heparin)

EDTA anticoagulant

Cytogenetics (2 mL)

Flow cytometry (2 mL)

Molecular Studies (2 mL)

Biopsy
- Touch imprint
- Wright Giemsa

Decalcified fixed paraffin section, H&E stain

THANK YOU
Rkanagal@mdanderson.org