WHO Update: Myelodysplastic syndromes

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Massachusetts General Hospital and Harvard Medical School
Overview of lecture

- Review the current WHO categorization of MDS entities
- Present proposed changes in the updated classification based on recently accumulated data
  - Impact how MDS entities are classified
  - Impact distinction between MDS and non-neoplastic conditions that may cause cytopenia
Myelodysplastic syndromes

- Clonal hematopoietic stem cell diseases
  - At diagnosis, the vast majority of hematopoietic cells are part of the neoplastic clone
  - Clone has recurring genetic abnormalities
- Ineffective hematopoiesis with one or more peripheral cytopenias
- Morphologic dysplasia of maturing hematopoietic elements
- Variable increase in myeloblasts (<20%)
  - May progress to AML with differing propensities depending on disease subtype
# WHO MDS subtypes

## No excess of blasts
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)

## Excess blasts
- Refractory anemia with excess blasts
  - RAEB1
  - RAEB2
Multimodality approach to MDS diagnosis and classification

Peripheral counts

Karyotype

Dysplasia and blasts
## Separating MDS disease subtypes

<table>
<thead>
<tr>
<th></th>
<th>Multilineage dysplasia</th>
<th>Ring sideroblasts</th>
<th>Blasts ≥5% or Auer Rods</th>
<th>Isolated del(5q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARS</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>RCUD</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>RCMD</td>
<td>Yes</td>
<td>Yes or No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MDS del(5q)</td>
<td>Yes or No</td>
<td>Yes or No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MDS-U</td>
<td>Yes or No</td>
<td>Yes or No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>RAEB1/2</td>
<td>Yes or No</td>
<td>Yes or No</td>
<td>Yes</td>
<td>Yes or No</td>
</tr>
</tbody>
</table>
New data in MDS

- Update of 1997 International Prognostic Scoring System (IPSS-R) published in 2012
  - Refinement of cytogenetic risk groups (5 vs 3)
  - More detailed use of cytopenias
  - MDS with <5% blasts now 2 groups
    - ≤2% and >2%–<5% blasts
- Accumulating data on utility of flow cytometry in MDS diagnosis and prognosis
- Identification of recurring point mutations in MDS that correlate with disease biology and outcome

Greenberg PL et al. Blood 2012;120:2454
How will this additional information be incorporated into MDS diagnosis?

Now...  

Dysplasia and blasts
Karyotype
Peripheral counts

... future?

Dysplasia and blasts
Karyotype
Peripheral counts
Flow cytometry
Mutations
Morphology: reproducibility of MDS diagnosis and classification

Some morphologic criteria may be difficult to apply
  – Accurate myeloblast and promonocyte enumeration
  – Reproducible evaluation of dysplasia

Requires high-quality material
  – Adequate (≥1.5 cm) bone marrow trephine
  – Well-prepared aspirate smears

Threshold for calling dysplasia

- Currently 10% of cells in any lineage
- No distinction between different specific dysplastic morphologies
- Dysplasia is not specific for MDS
  - Significant dysplasia in bone marrow of normal volunteers
  - Dysplastic changes are even more frequent in patients with non-neoplastic cytopenias
- Dysplasia is not always reproducible among pathologists

Can we do better than >10%?

<table>
<thead>
<tr>
<th>Morphological abnormalities&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cutoff values&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AUC</th>
<th>Cohen’s K-coefficient (inter-observer agreement)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythroid lineage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megaloblastoid changes</td>
<td>&gt; 5%</td>
<td>0.814, (P &lt; 0.001)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bi- or multinuclearity</td>
<td>&gt; 3%</td>
<td>0.679, (P &lt; 0.001)</td>
<td>0.87</td>
</tr>
<tr>
<td>Nuclear lobulation or irregular contours</td>
<td>&gt; 5%</td>
<td>0.698, (P &lt; 0.001)</td>
<td>0.84</td>
</tr>
<tr>
<td>Pyknosis</td>
<td>&gt; 5%</td>
<td>0.674, (P &lt; 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cytoplasmic fraying</td>
<td>≥ 7%</td>
<td>0.677, (P &lt; 0.001)</td>
<td>0.82</td>
</tr>
<tr>
<td>Ring sideroblasts</td>
<td>&gt; 5%</td>
<td>0.602, (P &lt; 0.001)</td>
<td>0.95</td>
</tr>
<tr>
<td>Ferritin sideroblasts</td>
<td>≥ 15%</td>
<td>0.650, (P &lt; 0.001)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>≥ 30%</td>
<td>0.719, (P &lt; 0.001)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Granulocytic lineage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>&gt; 3%</td>
<td>0.777, (P &lt; 0.001)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>&gt; 5%</td>
<td>0.723, (P &lt; 0.001)</td>
<td>0.92</td>
</tr>
<tr>
<td>Auer rods</td>
<td>≥ 1%</td>
<td>0.524, (P = 0.001)</td>
<td>0.90</td>
</tr>
<tr>
<td>Pseudo Pelger–Hüet anomaly</td>
<td>&gt; 3%</td>
<td>0.714, (P &lt; 0.001)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>&gt; 5%</td>
<td>0.814, (P &lt; 0.001)</td>
<td>0.87</td>
</tr>
<tr>
<td>Abnormal nuclear shape</td>
<td>≥ 7%</td>
<td>0.700, (P &lt; 0.001)</td>
<td>0.86</td>
</tr>
<tr>
<td>Neutrophil hypogranulation</td>
<td>&gt; 3%</td>
<td>0.791, (P &lt; 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>&gt; 5%</td>
<td>0.821, (P &lt; 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Megakaryocytic lineage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micromegakaryocytes</td>
<td>&gt; 5%</td>
<td>0.916, (P &lt; 0.001)</td>
<td>0.88</td>
</tr>
<tr>
<td>Small binucleated megakaryocytes</td>
<td>&gt; 5%</td>
<td>0.845, (P = 0.001)</td>
<td>0.81</td>
</tr>
<tr>
<td>Megakaryocytes with multiple separated nuclei</td>
<td>&gt; 5%</td>
<td>0.750, (P &lt; 0.001)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypolobated or monolobar megakaryocytes</td>
<td>&gt; 5%</td>
<td>0.646, (P &lt; 0.001)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Della Porta MG Leukemia 2014;29:66
Handling of blast and dysplasia thresholds in update

- Dysplasia threshold will be kept at 10% for all lineages, but note that 30% or 40% level for megakaryocytes may be more specific.

- Provide more detailed definitions of dysplasia and emphasize morphologic overlap with non-MDS mimics (always a potential pitfall).

- There will not be a 0-2% BM blast group:
  - Distinguishing 0-2% from >2%-<5% blasts would be difficult to apply reproducibly in practice.
  - Always report the exact blast count! (not “<5%”)

Impact of the explosive advance of molecular genetics on MDS

Can mutations be used to diagnose MDS?

Should MDS entities be defined by common molecular lesions or by common morphologic/clinical features?

Major caveats

- Molecular genetic testing availability is not keeping up with its increasing relevance
- Data is actively accumulating ("moving target")
Somatic mutations in MDS: a barrage of new information

Ribosomal proteins: *RPS14*
Epigenetic regulators: *TET2, ASXL1*
RNA splicing: *SF3B1, SRSF2, U2AF1*
Transcription factors: *RUNX1, ETV6*
Tyrosine kinase signaling: *RAS*
Tumor suppressor genes: *TP53*
Relationship between number of mutations and outcome in MDS

Papaemmanuil E Blood 2013;122:3616
Prognostic value of specific mutations

Bejar NEJM 2011;364:2496

TP53, EZH2, ETV6, RUNX1, or ASXL1 mutations confer adverse prognosis

C

- Low risk, mutation absent (N=87)
- Low risk, mutation present (N=23)
  P<0.001
- Intermediate-1 risk (N=185)
SF3B1: a spliceosome gene where mutation conveys favorable prognosis

- SF3B1 point mutation is strongly correlated with the presence of ring sideroblasts
- SF3B1 mutation confers a survival advantage in MDS
  - Uncertain how this is influenced by the presence of multilineage dysplasia
  - Does not appear to impact survival of RAEB patients

SF3B1 mutation is associated with highly differential gene expression

Gerstung M Nature Comm 2015;6:5901
New handling of MDS with ring sideroblasts

- MDS with multilineage dysplasia and ring sideroblasts will be reinstated ("RCMD-RS")
- MDS cases with SF3B1 mutation can be classified as RARS or RCMD-RS if any ring sideroblasts are present
  - Will not require ≥15% RS in the presence of SF3B1 mutation
- Presence of SF3B1 mutation or RS will not affect RAEB or MDS with isolated del(5q)
MDS with isolated del(5q): new data

No adverse effect with one additional cytogenetic abnormality

*TP53 mutation confers poor prognosis to del(5q) patients treated with lenalidomide

Proposed changes to MDS del(5q) in light of new information

- Broaden definition to allow one additional cytogenetic abnormality
  - Excluding high-risk abnormalities, e.g. -7
- Suggest TP53 mutation test or p53 immunostain in MDS

Exclusions
- Increased blasts in blood or marrow
- Cases with significant granulocytic dysplasia

MDS, unclassifiable (MDS-U): the group nobody likes!

- **RCUD with pancytopenia**
  
  *Cytopenias must be below IPSS-R levels:*
  
  ANC<0.8 x 10⁹/L, HGB<10 g/dL, PLT<100 x 10⁹/L

- **RCUD with exactly 1% peripheral blood blasts**
  
  *1% blasts must be measured on at least two separate occasions*

- **MDS without excess blasts or dysplasia, but with an MDS-defining cytogenetic abnormality**
Can mutations be used to diagnose MDS in 2015?

Beware: 10% of healthy individuals >65 years harbor somatic MDS-type mutations in hematopoietic cells!
- Mostly $DNMT3A$, $TET2$, $ASXL1$, $TP53$, $JAK2$, $SF3B1$
- Allele burden typically 10-20% in blood
- Associated with increased risk of subsequent hematologic malignancy and death

Presence of mutations is not sufficient to diagnose MDs: further study is needed
- In the future, multiple mutations, particular combinations of mutations, and/or high allele burden may provide more specificity for diagnosing MDS

Can flow cytometry aberrancies be used to diagnose MDS in 2015?

- Accumulating evidence suggests that abnormal flow cytometry patterns predict MDS with good sensitivity/specificity
- Specific panels should be carefully chosen and validated according to published guidelines
- Flow cytometry results should be integrated with the bone marrow morphology report
- Will still only be considered as “supportive” of MDS and will not alone be sufficient for making a primary MDS diagnosis

The border between MDS and AML: Acute erythroid leukemia (AEL, M6A)

- Erythroid elements are $\geq 50\%$ of marrow cells
- Myeloblasts are $\geq 20\%$ of non-erythroid cells
- AEL is a subtype of AML, but recent data suggest a closer relationship to MDS
  - Often occurs as a “progression” of prior MDS
  - Morphologic dysplasia is characteristic
  - Genetic abnormalities are more similar to MDS than to de novo AML

  *TP53* mutation common, *FLT3/NPM1* mutations rare

Blast counting in myeloid neoplasms with erythroid predominance

Small changes in blast percentages can change diagnosis, with major clinical impact

?RAEB<>AEL?

Blasts >20% of non-erythroid
Blast counting in myeloid neoplasms with erythroid predominance

- Small changes in blast percentages can change diagnosis, with major clinical impact
- Erythroids may fluctuate due to therapy, metabolic deficiencies, or EPO effects, changing diagnosis

?RAEB<>AEL?

>20% of non-erythroid
Non-erythroid blast counting will be eliminated in all myeloid neoplasms

- Cases with ≥50% erythroids and 5-19% blasts will be considered as RAEB, no longer AML
  - Cases with ≥20% blasts and ≥50% erythroids will still be classified as AML (most are AML-MRC)
  - Pure erythroleukemia will remain in AML

- Will achieve consistency of blast counting across all myeloid neoplasms
  - Avoid abrupt change when erythroids reach 50%

- Will link AEL with MDS, with which it shares morphologic and genetic features
Proposed new MDS nomenclature

- MDS with single lineage dysplasia (MDS-SLD) = RCUD
- MDS-SLD with ring sideroblasts = RARS
- MDS with multilineage dysplasia = RCMD
  - MDS-MLD with ring sideroblasts = RCMD-RS
- MDS with isolated* del(5q) = RCUD
- MDS with excess blasts
  - MDS-EB1 = RAEB-1
  - MDS-EB2 = RAEB-2
- MDS, unclassifiable (MDS-U)

* WHO 2008 translation
Why change MDS nomenclature?

- WHO scheme classifies based on dysplasia and blast counts, not cytopenia
  - Cytopenias are captured in IPSS-R system
- Type of dysplasia often does not agree with the cytopenic lineage in RCUD
  - Cannot predict peripheral counts from dysplasia

Remove reference to anemia/cytopenia from names and just call MDS directly!

*Myelodysplastic syndrome, consistent with refractory cytopenia with unilineage dysplasia (refractory thrombocytopenia)*

*Myelodysplastic syndrome, best classified as refractory anemia with excess blasts-1*

*Myelodysplastic syndrome with single lineage dysplasia*

*Myelodysplastic syndrome with excess blasts-1*
CMML: Issues and new data

- Myeloid neoplasm with persistent blood monocytosis (absolute count >1 x 10⁹/L)
  - <20% blasts/promonocytes
  - Dysplasia usually present, karyotype usually normal

- Challenges in diagnosis: CMML versus MDS, reactive monocytosis, or monocytic AML

- Common pattern of co-mutation in epigenetic modifier and RNA splicing gene
  - $TET2 + SRSF2$ in 30-35% of CMML (vs 3% of MDS)
  - Either $TET2$, $SRSF2$, or $ASXL1$ mutation in 90%
  - $ASXL1$ mutation confers poor prognosis independent of karyotype risk

Monocytic cells: poor reproducibility in counting blast equivalents
Updates to CMML

- Mutations will help support the diagnosis (particularly $TET2+SRSF2$) and provide prognostic information ($ASXL1$)
  - Mutations alone not sufficient to diagnose CMML

- Clarify criteria for promonocytes to help distinguish CMML from monocytic AML
  - Presence of an $NPM1$ mutation or 11q23 rearrangement may herald rapid progression to AML and patient should be followed closely

RARS-T: now promoted to a full entity in MDS/MPN!

**MPN-like**
- Clinical
  - Thrombocytosis
  - Need for cytoreduction
- Morphologic
  - Large megakaryocytes with bulbous nuclei
- Genetic
  - JAK2 mutation (50-60%)
  - Rare CALR/MPL

**MDS-like**
- Clinical
  - Macrocytic anemia
  - Transfusion requirement
- Morphologic
  - Erythroid dysplasia
  - Ring sideroblasts
- Genetic
  - SF3B1 mutation (80-90%)

Conclusions: MDS diagnosis will continue to rely on multiple modalities

- Recent study analyzed the impact of various factors on outcome in 124 MDS patients
- Optimal model was achieved by combining all information

Gerstung M Nature Comm 2015;6:5901
Summary: MDS revision

No excess of blasts

- MDS with single lineage dysplasia
- MDS with single lineage dysplasia and RS
- MDS with multilineage dysplasia
  - with RS
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)

Excess blasts

- MDS with excess blasts
  - MDS with excess blasts-1
  - MDS with excess blasts-2
  - Either ≥15% RS or any RS and SF3B1 mutation
  - One additional (non-high-risk) chromosomal abnormality allowed
  - Recommend testing for TP53 mutation
  - Cases with significant granulocytic dysplasia excluded
Summary: MDS revision

**No excess of blasts**
- MDS with single lineage dysplasia
- MDS with single lineage dysplasia and RS
- MDS with multilineage dysplasia
  - with RS
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)

**Excess blasts**
- MDS with excess blasts
  - MDS with excess blasts-1
  - MDS with excess blasts-2

  - Now will include most cases previously classified as acute erythroid leukemia, categorized based on blast % of total marrow cells
Summary: MDS/MPN revision

- **Chronic myelomonocytic leukemia**
- MDS/MPN-U
- Atypical CML, *BCR-ABL1* negative
- Juvenile myelomonocytic leukemia
- Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T)

- Mutation profile helpful in supporting diagnosis and providing prognosis
  - Cases with NPM1 mutation or 11q23 rearrangement should be followed carefully for AML
  - Emphasize careful blast/promonocyte/monocyte count to distinguish from AML

- Moved from a provisional to a full entity
- Common co-mutation of JAK2 and SF3B1