Myelodysplastic syndromes: revised WHO classification and distinction from non-neoplastic conditions

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Myelodysplastic syndromes

- Clonal hematopoietic stem cell neoplasms with *ineffective* hematopoiesis and intact maturation
  - Peripheral blood cytopenias
  - Cytologic dysplasia of hematopoietic elements
- Varying propensity to develop maturation arrest in hematopoietic cells, with accumulation of blasts and progression to AML
Ineffective hematopoiesis
Intact maturation

MDS

MDS/MPN

MPN

- Cytopenias
- Dysplastic morphology
- Altered cell function
- No organomegaly

- Elevated counts
- Non-dysplastic morphology
- Normal cell function
- Often splenomegaly
The spectrum of MDS

- Indolent “low-grade” subtypes
  - Low blast counts
  - Typically low risk of progression to AML
  - Morbidity and mortality due to cytopenias and/or complications of transfusion

- Aggressive subtypes
  - Higher blast counts, genetic instability
  - Often rapidly progress to AML
“Low-grade” MDS

“High-grade” MDS
Challenges in MDS diagnosis

- Does the patient have a neoplasm?
- Should the patient be treated for MDS or should another diagnosis be sought?

- Risk-adapted therapy according to prognosis
- Should the patient receive induction or other intensive chemotherapy with a goal of remission?
Components of MDS diagnosis and classification (2016 WHO)

Dysplasia and blasts are a sine qua non of MDS.

90% of MDS cases have a demonstrable clonal genetic abnormality.

Dysplasia is defining feature of MDS.
Information needed by pathologist to diagnose MDS

• Clinical history
  – Full CBC and WBC differential results
  – Knowledge of duration of cytopenias and possible other causes of cytopenia

• Morphology review
  – Blood smear
  – Bone marrow aspirate or touch prep
    • Wright-Giemsa and iron stains
  – Bone marrow biopsy

• Complete bone marrow karyotype
Complications in defining cytopenia

### ANC x 10^9/L
- <1.0
- 1.1
- 1.2
- 1.3
- 1.4
- 1.5
- 1.6
- 1.7
- 1.8
- 1.9
- ≥2.0

### HGB g/dL
- 8.0
- 9.0
- 10.0
- 11.0
- 12.0
- 13.0
- 14.0

- <10 (WHO/IPSS)
- <11 (2007 MDS Consensus)
- <12/13 (WHO anemia definition)

### Platelets x 10^9/L
- 80
- 90
- 100
- 110
- 120
- 130
- 140
- 150
- 160
- 170
- 180

- <100 (WHO/IPSS)
- <150 (normal reference)

Megakaryocyte dysplasia

- Small size
- Hypo/misomyonucleation
- Separated nuclear lobes

Micromegakaryocytes
Granulocytic dysplasia

- Bilobed pseudo Pelger-Huet nucleus
- Nuclear hypersegmentation or other abnormal nuclear shape
- Cytoplasmic hypogranulation or uneven granulation
- Normal poly
Erythroid dysplasia

- Cytoplasmic vacuolization
- Megaloblastoid change (nuclear:cytoplasmic asynchrony)
- Bi- or multi-nucleation
- Nuclear budding and nuclear irregularities
Dysplasia assessment

- Threshold of 10% of cells in any lineage
- No distinction between different types of dysplastic morphologies
- Dysplasia is not always reproducible, even among experienced hematopathologists
- 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

## Specificity of dysplastic findings

<table>
<thead>
<tr>
<th>Morphological abnormalities</th>
<th>Cutoff values</th>
<th>AUC</th>
<th>Cohen’s K-coefficient (inter-observer agreement)</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></td>
</tr>
<tr>
<td>Pyknosis</td>
<td>&gt; 3%</td>
<td>0.674, P &lt; 0.001</td>
<td>0.84</td>
</tr>
<tr>
<td>Cytoplasmic fraying</td>
<td>&gt; 7%</td>
<td>0.602, P &lt; 0.001</td>
<td>0.82</td>
</tr>
<tr>
<td>Ring sideroblasts</td>
<td>&gt; 5%</td>
<td>0.650, P &lt; 0.001</td>
<td>0.95</td>
</tr>
<tr>
<td>Ferritin sideroblasts</td>
<td>≥ 15%</td>
<td>0.719, P &lt; 0.001</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>≥ 30%</td>
<td>0.670, P &lt; 0.001</td>
<td></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>Auer rods</td>
<td>&gt; 5%</td>
<td>0.723, P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Pseudo Pelger–Hüet anomaly</td>
<td>≥ 1%</td>
<td>0.524, P = 0.001</td>
<td>0.90</td>
</tr>
<tr>
<td>Abnormal nuclear shape</td>
<td>&gt; 3%</td>
<td>0.714, P &lt; 0.001</td>
<td>0.87</td>
</tr>
<tr>
<td>Neutrophil hypogranulation</td>
<td>&gt; 5%</td>
<td>0.814, P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 7%</td>
<td>0.700, P &lt; 0.001</td>
<td>0.86</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></td>
</tr>
<tr>
<td>Hypolobated or monolobar megakaryocytes</td>
<td>&gt; 5%</td>
<td>0.646, P &lt; 0.001</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Della Porta MG Leukemia 2014;29:66
Can we develop a more objective way to diagnose MDS?

• Flow cytometry abnormalities
  – Hematopoiesis in most MDS cases is phenotypically abnormal

• Genetic abnormalities
  – Karyotype abnormalities (only 50% of cases)
  – Sub-karyotypic acquired genetic alterations
    • Microdeletions (SNP array)
    • Mutations (next-generation sequencing)
Flow cytometry assessment of MDS

- Abnormal flow cytometry patterns predict MDS with good sensitivity and specificity
- WHO 2016 and ELN guidelines do not permit a diagnosis of MDS solely based on flow cytometry
  - Considered ‘supportive’ of a diagnosis
  - More data needed on reactive conditions

Abnormalities in blasts

Abnormalities in maturing elements

MDS-defining cytogenetic abnormalities (WHO 2016)

<table>
<thead>
<tr>
<th>Unbalanced</th>
<th>Primary MDS</th>
<th>Therapy-related MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7 or del(7q)</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>-5 or del(5q)</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>3-5%</td>
<td></td>
</tr>
<tr>
<td>-13 or del(13q)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(9q)</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td>1-2%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Balanced</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;16)(q23;p13.3)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>t(2;11)(p21;q23)</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>inv(3)(q21q26.2)</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>t(6;9)(p23;q34)</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Note that +8, -Y, and del(20q) can occur in non-neoplastic conditions and are not MDS-defining
Somatic mutations in MDS: a lot 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: $TP53$

Some genetic abnormality is present in 80-92% of MDS cases
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”)
“Clonal Hematopoiesis of Indeterminate Potential” (CHIP)

- A proportion of apparently healthy aging individuals harbor somatic MDS-type mutations in hematopoietic cells
  - *DNMT3A, TET2, ASXL1, TP53, JAK2, SF3B1*
  -Allele burden typically 10-20% in blood, can be higher
  -Associated with increased risk of subsequent hematologic malignancy and death from other causes
  -Many patients never develop cytopenias or MDS even after many years of followup

Both CHIP and MDS affect older individuals, but CHIP is far more frequent.

CHIP: “Clonal Hematopoiesis of Indeterminate Potential”

What is sufficient to diagnose MDS in a cytopenic patient in 2016?

<table>
<thead>
<tr>
<th>Observation</th>
<th>Sufficient to diagnose MDS in isolation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplastic morphology (≥10%)</td>
<td>Yes, provided possible secondary causes of cytopenia and dysplasia are excluded clinically</td>
</tr>
<tr>
<td>Excess marrow blasts (≥5%)</td>
<td>Yes, provided marrow recovery or growth factor effect are excluded</td>
</tr>
<tr>
<td>Cytogenetic abnormality</td>
<td>Yes, provided it is on the WHO list of ‘approved’ abnormalities*</td>
</tr>
<tr>
<td>Flow cytometry abnormality</td>
<td>No, but can support an MDS diagnosis suspected by other observations</td>
</tr>
<tr>
<td>MDS-type mutation</td>
<td>No, these can be found in normal individuals and more study is needed (“Clonal hematopoiesis of indeterminate potential”)</td>
</tr>
</tbody>
</table>

*Specifically excluded are –Y, +8, and del(20q)
Morphologic diagnosis of MDS remains subjective

- **Morphologic dysplasia**
  - ↑ Lineages involved
  - ↑ Number of dysplastic forms
  - ↑ Severity of dysplasia

- **Severity and persistence of cytopenia(s)**

- **Unexplained ↑ MCV**

- **Flow cytometry abnormalities**

- **MDS-type mutations**

- **Younger patients**

- **Co-morbid conditions**

- **Paucity of clinical history**
Challenges in MDS diagnosis

- Non-neoplastic causes of cytopenia
  -- Other neoplasms
  -- Inherited
  -- Extrinsic factors

- Risk-adapted therapy according to prognosis

- Does the patient have a neoplasm?

- Should the patient be treated for MDS or should another diagnosis be sought?

- Should the patient receive induction or other intensive chemotherapy with a goal of remission?
## Prognostic schemes in MDS

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>Yes: single versus multilineage and ring sideroblasts</td>
<td>No</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>Yes: Pancytopenia is only defining feature</td>
<td>Yes: both number and depth of cytopenias</td>
</tr>
<tr>
<td>Blast % in blood</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blast % in bone marrow</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Yes: isolated del(5q) is the only defining feature</td>
<td>Yes, 5 prognostic groups</td>
</tr>
<tr>
<td>Molecular genetic abnormalities</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Flow cytometry abnormalities</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Revised International Prognostic Scoring System of MDS

Greenberg PL et al. Blood 2012;120:2454
Bone marrow blast percentage strongly influences overall survival in MDS

- 2% blast threshold will not be adopted by WHO
- Precise blast count should be specified in report so that IPSS-R can be applied

Greenberg PL et al. Blood 2012;120:2454
Role of blast estimation in the biopsy

- In some situations, the core biopsy blast count may be more accurate than the aspirate count
  - Hypocellular marrow
  - Fibrotic marrow
  - Technically poor aspirate smear
- CD34 immunostain may be effectively used to estimate blasts in the biopsy/clot section
- Some experts advocate performing CD34 on all bone marrow biopsy biopsies where MDS is a diagnostic consideration
Prognostic influence of cytogenetic abnormalities in MDS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Cytogenetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>Single del(11q) or -Y</td>
</tr>
</tbody>
</table>
| Good          | Normal del(5q)(single or with 1 other)  
Single del(12p) or del(20q) |
| Intermediate  | +8, i(17q), +19, single del(7q)  
Any other single or double |
| Poor          | -7, inv(3), t(3q), del(3q)  
del(7q) with 1 other  
3 separate abnormalities |
| Very poor     | 4 or more separate abnormalities (complex)                                             |

### WHO MDS subtypes (2008)

<table>
<thead>
<tr>
<th>No excess of blasts</th>
<th>Excess blasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Refractory anemia with ring sideroblasts (RARS)</td>
<td>• Refractory anemia with excess blasts</td>
</tr>
<tr>
<td>• Refractory cytopenia with unilineage dysplasia (RCUD)</td>
<td>• RAEB1</td>
</tr>
<tr>
<td>• Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>• RAEB2</td>
</tr>
<tr>
<td>• MDS with isolated del(5q)</td>
<td></td>
</tr>
<tr>
<td>• MDS, unclassifiable (MDS-U)</td>
<td></td>
</tr>
</tbody>
</table>
# MDS classification: new terminology

## WHO 2016

- **MDS with single lineage dysplasia (MDS-SLD)**
- **MDS with multilineage dysplasia (MDS-MLD)**
- **MDS with ring sideroblasts**
  - MDS-RS with single lineage dysplasia (MDS-RS-SLD)
  - MDS-RS with multilineage dysplasia (MDS-RS-MLD)
- **MDS with isolated del(5q)**
- **MDS, unclassifiable (MDS,U)**
- **MDS with excess blasts (MDS-EB)**
- **Refractory cytopenia of childhood (RCC)(provisional)**

## WHO 2008

- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS,U)
- Refractory anemia w/excess blasts (RAEB)
- Refractory cytopenia of childhood (RCC)(provisional)
Main new data incorporated into 2016 WHO Classification of MDS

• Significance of point mutations
  – Large body of information confirm significant impact of mutations on prognosis
  – Most data is still too immature to determine how to incorporate mutations into existing primarily morphologic classification

• New data help refine definition of MDS with isolated del(5q)

• Elimination of acute erythroid leukemia, with inclusion of most cases in MDS with excess blasts
MDS with isolated del(5q)
MDS with isolated del(5q): 2008 definition

- Del(5q) is only cytogenetic abnormality
- Blasts <5% in bone marrow, <1% in blood
- Can have any cytopenias; often thrombocytosis
- Can have uni- or multilineage dysplasia
  - Typically striking dysplasia of megakaryocytes and relative erythroid hypoplasia
- Favorable prognosis and excellent response to lenalidomide
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
P53 immunohistochemistry correlates well with presence of *TP53* mutation

Strongly correlated with poor prognosis in all type of MDS

Cleven AJ et al. Mod Pathol 2015;28:552
Changes to MDS del(5q) in the 2016 update

• Broaden definition to allow one additional cytogenetic abnormality (except -7 or del7q)
• Suggest *TP53* mutation test or p53 immunostain for prognostic information
• Any cases with increased blasts in blood or bone marrow are still excluded from the MDS del(5q) category

Ring sideroblasts: erythroid forms with aberrant iron accumulation in mitochondria encircling the nucleus
**SF3B1**: the most commonly mutated gene in MDS

- RNA splicing factor
- Mutation strongly correlates with ring sideroblasts
- Appears to be an early founding event in MDS
- Confers a survival advantage

SF3B1 mutation is associated with highly differential gene expression

Includes downregulation of ABCB7 gene due to altered exon usage

New handling of MDS with ring sideroblasts in WHO 2016

• MDS with ring sideroblasts (MDS-RS) will be broadened to include:
  – Traditional RARS (single erythroid lineage dysplasia)
  – Cases with multilineage dysplasia
  – Cases with \textit{SF3B1} mutation and \( \geq 5\% \) RS
    • If \textit{SF3B1} mutation status is negative or unknown, \( \geq 15\% \) RS will be required

• Presence of \textit{SF3B1} mutation or RS will not affect MDS with excess blasts or isolated del(5q)
New WHO Classification of MDS (<5% blasts)

• **MDS with single lineage dysplasia (MDS-SLD)**
  – Only one lineage is dysplastic
  – 1-2 cytopenias
    • Dysplastic lineage may not be the same as the cytopenia!
  – Good prognosis

• **MDS with multilineage dysplasia (MDS-MLD)**
  – Two or three dysplastic lineages
  – 1-3 cytopenias
  – Intermediate prognosis
New WHO Classification of MDS (<5% blasts)

- MDS with ring sideroblasts (MDS-RS)
  - ≥15% ring sideroblasts on iron stain
    - OR
  - ≥ 5% ring sideroblasts and an SF3B1 mutation
  - Usually few other mutations and simple karyotype
  - Further divided based on single (MDS-RS-SLD) versus multilineage (MDS-RS-MLD) dysplasia
  - Prognosis appears to be driven by multilineage dysplasia and other mutations
New WHO Classification of MDS (<5% blasts): MDS, unclassifiable

- MDS with SLD but with pancytopenia
  
  Three cytopenias below IPSS levels:
  ANC<1.8 x 10⁹/L, HGB<10 g/dL, PLT<100 x 10⁹/L

- MDS-SLD,-MLD, del(5q) with exactly 1% PB blasts

  1% PB blasts must be measured on at least two separate occasions

- MDS without excess blasts or dysplasia, but with an MDS-defining cytogenetic abnormality
MDS with excess blasts (MDS-EB)

- ≥5% blasts in marrow or ≥2% blasts in blood
  - Subdivided into MDS-EB-1 and MDS-EB-1 based on marrow and blood blast levels
- Increased blasts are a very strong indicator of aggressive behavior in MDS, independent of cytogenetics, cytopenias, and mutations
- CD34 immunostaining useful in cases with fibrosis or poor aspirate
Challenges in MDS diagnosis

- Does the patient have a neoplasm?
- Should the patient be treated for MDS or should another diagnosis be sought?

Risk-adapted therapy according to prognosis

- Should the patient receive induction or other intensive chemotherapy with a goal of remission?
Blast counting in myeloid neoplasms with erythroid predominance (≥50% erythroids)

- 2008 WHO classification rule allows acute erythroid leukemia (AEL) diagnosis if blasts comprise ≥20% of non-erythroid cells if erythroids are ≥50% of marrow cells

MDS-EB or AEL?

- Blasts
- >20% of non-erythroid
Controversies in blast counting.

Dysplastic erythroid precursors in the myelodysplastic syndromes and the acute myeloid leukemias: Is there biologic significance? (How should blasts be counted?)

Acute erythroid leukemia with <20% bone marrow blasts is clinically and biologically similar to myelodysplastic syndrome with excess blasts.

New WHO 2016 recommendations for blast counting

• Blasts in BM always counted as % of total cells, never as % of non-erythroid cells
• Myeloid neoplasms with ≥50% erythroids and with blasts <20% all cells are now classified as MDS-EB, even if blasts are ≥20% of the non-erythroid cells
  – Merged most cases previously diagnosed as acute erythroleukemia into MDS-EB
  – Pure erythroid leukemia will remain in AML

# 2016 WHO Classification of MDS-1

<table>
<thead>
<tr>
<th></th>
<th>Dysplastic lineages</th>
<th>Cytopenias</th>
<th>RS as % of erythroids</th>
<th>BM and PB blasts</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-SLD</td>
<td>1</td>
<td>1 or 2&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;15%/&lt;5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;5% BM, &lt;1% PB&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Any&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS-MLD</td>
<td>2 or 3</td>
<td>1-3</td>
<td>&lt;15%/&lt;5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;5% BM, &lt;1% PB&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Any&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS-RS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with SLD</td>
<td>1</td>
<td>1 or 2</td>
<td>≥15%/≥5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;5% BM, &lt;1% PB&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Any&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>with MLD</td>
<td>2 or 3</td>
<td>1-3</td>
<td>≥15%/≥5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;5% BM, &lt;1% PB&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Any&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>1-3</td>
<td>1 or 2</td>
<td>None or any</td>
<td>&lt;5% BM, &lt;1% PB&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Del(5q) alone or with 1 other abnormality (except -7/del7q)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Note that cytopenic lineage frequently does not correlate with dysplastic lineage in MDS-SLD

<sup>2</sup>If *SF3B1* mutation is present

<sup>3</sup>Also no Auer rods

<sup>4</sup>Unless fulfills all criteria for MDS with isolated del(5q)

# 2016 WHO Classification of MDS-2

<table>
<thead>
<tr>
<th></th>
<th>Dysplastic lineages</th>
<th>Cytopenias</th>
<th>RS as % of erythroids</th>
<th>BM and PB blasts</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-EB</td>
<td>0-3</td>
<td>1-3</td>
<td>None or any</td>
<td>5-9% BM or 2-4% PB</td>
<td>Any</td>
</tr>
<tr>
<td>MDS-EB1</td>
<td>0-3</td>
<td>1-3</td>
<td>None or any</td>
<td>10-19% BM or 5-19% PB or Auer rods</td>
<td>Any</td>
</tr>
<tr>
<td>MDS, unclassifiable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with 1% PB blasts</td>
<td>1-3</td>
<td>1-3</td>
<td>None or any</td>
<td>&lt;5% BM, =1% PB</td>
<td>Any</td>
</tr>
<tr>
<td>with SLD and pancytopenia</td>
<td>1</td>
<td>3</td>
<td>None or any</td>
<td>&lt;5% BM, &lt;1% PB</td>
<td>Any</td>
</tr>
<tr>
<td>based on karyotype</td>
<td>0</td>
<td>1-3</td>
<td>&lt;15%</td>
<td>&lt;5% BM, &lt;1% PB</td>
<td>MDS-defining</td>
</tr>
</tbody>
</table>

1. BM blast percentage always derived from all nucleated cells, even if erythroids are ≥50%
2. Also no Auer rods
3. 1% PB blasts must be documented on at least 2 separate occasions
Special situations in MDS

• Hypoplastic MDS
  – About 10% of cases
  – Differential diagnosis with aplastic anemia
  – CD34 and CD61 immunostains of biopsy

• MDS with fibrosis
  – 10-15% of cases
  – Differential diagnosis with MPN and MDS/MPN
  – CD34 and CD61 immunostains of biopsy
  – Adverse prognosis

• MDS in children
  – Refractory cytopenia of childhood still a provisional entity in 2016 WHO
    – Usually hypoplastic, differential diagnosis with aplastic anemia
    – Different mutational profile from adult MDS
  – MDS-EB and therapy-related MDS also occur in children

Hypoplastic MDS

CD61

MDS with fibrosis

Reticulin
Myelodysplastic/myeloproliferative neoplasms (2008)

• Most often an elevated peripheral counts + dysplasia and other cytopenias

• Specific entities
  – Chronic myelomonocytic leukemia (CMML)
  – Atypical chronic myeloid leukemia (aCML)
  – Juvenile myelomonocytic leukemia (JMML)
  – Unclassifiable (MDS/MPN-U)
    • Refractory anemia with ring sideroblasts and marked thrombocytosis (RARS-T)

• Generally poorer prognosis than ‘pure’ MPN
Chronic myelomonocytic leukemia

• Peripheral blood
  – Persistent monocytosis: ≥10% monocytes in blood with ≥1 x 10⁹/L absolute monocytes

• Bone marrow
  – Hypercellular with dysplasia in one or more lineages
  – Blasts and promonocytes are <20%

• Clinical features
  – White blood count may be increased or decreased; other cytopenias usually present
  – May or may not have splenomegaly
Chronic myelomonocytic leukemia
peripheral blood
Chronic myelomonocytic leukemia: Clinical and genetic features

• 60-80% have normal karyotype
  – Must exclude t(5;12) (PDGFRB fusion) in cases with eosinophilia

• Distinctive mutation profile: combination of epigenetic modifier and RNA splicing gene
  – TET2, SRSF2, or ASXL1 mutated in 80-90%
  – ASXL1 associated with adverse prognosis

• Median survival 2-3 years
  – 15-30% progress to AML

Itzykson R et al. J Clin Oncol 2013;31:2428,
CMML: WHO 2016 groups

• Stratification based on white blood cell count
  – “Proliferative type”: WBC count ≥13 x 10^9/L
  – “Dysplastic type”: WBC count <13 x 10^9/L
  – Differences in mutation profile and prognosis

• Stratification based on blast/promonocyte %
  – CMML-0: <5% BM blasts, <2% PB blasts
  – CMML-1: 5-9% BM blasts or 2-4% PB blasts
  – CMML-2: 10-19% BM blasts or 5-19% BP blasts (or presence of any Auer rods)

Monocytic cells

Monoblasts

Promonocytes

Monocytes

BLAST EQUIVALENTS
# MDS/MPN overlap diseases

<table>
<thead>
<tr>
<th></th>
<th>CMML</th>
<th>Atypical CML</th>
<th>MDS/MPN-U</th>
<th>MDS/MPN-RS-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>Myeloids</td>
<td>Myeloids (severe)</td>
<td>Variable</td>
<td>Erythroids (RS)</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>Any</td>
<td>Any or none</td>
<td>Any or none</td>
<td>Anemia</td>
</tr>
<tr>
<td>Proliferation</td>
<td>Monos ≥1 x 10⁹/L</td>
<td>WBC ≥13 x 10⁹/L</td>
<td>PLT ≥450 x 10⁹/L or WBC ≥13 x 10⁹/L</td>
<td>PLT ≥450 x 10⁹/L</td>
</tr>
<tr>
<td>Genetics</td>
<td>TET2 50%</td>
<td>TET2 30%</td>
<td>TET2 30%</td>
<td>SF3B1 85%</td>
</tr>
<tr>
<td></td>
<td>ASXL1 45%</td>
<td>SETBP1 25%</td>
<td>RUNX1 15%</td>
<td>JAK2 60%</td>
</tr>
<tr>
<td></td>
<td>SRSF2 40%</td>
<td>ASXL1 25%</td>
<td>SETBP1 10%</td>
<td>TET2 25%</td>
</tr>
<tr>
<td></td>
<td>RUNX1 15%</td>
<td>NRAS 20%</td>
<td>NRAS 10%</td>
<td>DNMT3A 15%</td>
</tr>
<tr>
<td></td>
<td>CBL 15%</td>
<td>EZH2 15%</td>
<td>CBL 10%</td>
<td>MPL 10%</td>
</tr>
<tr>
<td></td>
<td>SETBP1 10%</td>
<td>ETKN1 9%</td>
<td>EZH2 10%</td>
<td>ASXL1 10%</td>
</tr>
<tr>
<td></td>
<td>ETKN1 2%</td>
<td>CBL 8%</td>
<td>JAK2 20%</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>31 months</td>
<td>12 months</td>
<td>22 months</td>
<td>88-120 months</td>
</tr>
<tr>
<td>Prognostic factors</td>
<td>Karyotype ASXL1 mut Blasts ≥10%</td>
<td>Karyotype Higher WBC Increased blasts</td>
<td>Karyotype</td>
<td>SF3B1 mut JAK2 mut</td>
</tr>
</tbody>
</table>

Conclusions

• New sequencing technologies have introduced the potential for more objective MDS diagnosis
  – Earlier diagnosis, better risk-stratification, targeted therapies
  – Distinction between MDS and “CHIP” is problematic and still must be clarified

• The 2016 revised WHO Classification of MDS and MDS/MPN has incorporated changes
  – Better define existing entities
  – Altered definitions that recategorize cases based on accumulated clinicopathologic data
  – Classification will continue to evolve!