What is MDS? How do we predict prognosis?

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Division of Hematology/Oncology
Internal Medicine
November 9th, 2019
How Does MDS Happen?

- All blood cells come from HSCs
- HSCs are the only long lived cells in the blood system
- HSCs develop mistakes in DNA with age or exposure to toxins
- MDS happens when mistakes in DNA impair the function of HSCs
The Myelodysplastic Syndromes
Clinical Features

- Peripheral blood cytopenias
- Risk for progression to acute leukemia (AML)
- But...
  - Not all MDS cases will progress to AML
  - Not cytopenias are from MDS
  - Not all MDS cases are alike - it is “heterogenous”
The Myelodysplastic Syndromes - Key Features

- Clonal disorders
  - All starts with one abnormal cell (a clone)
- Impaired differentiation
  - Immature blood cells don’t grow up correctly
- Dysplasia
  - Maturing blood cells look abnormal
- Increased apoptosis
  - More cell death
The Myelodysplastic Syndromes - Key Features

- Blasts
  - Immature cells
  - Normal to have up to 3-5%
  - If these immature cells become >20%, we call it acute myeloid leukemia (AML)
  - Only ~1/3\(^{rd}\) of MDS progresses to AML
Diagnosis of the Myelodysplastic Syndromes

- Cytopenias
  - Hemoglobin <10 g/dL
  - Absolute Neutrophil Count <1.8 x 10^9/L
  - Platelets <100 x 10^9/L

- 1. Dysplasia in >10% of cells in at least one lineage
- 2. MDS-defining cytogenetic (chromosome) abnormalities
- 3. >5% blasts

MDS Defining Cytogenetic Abnormalities

<table>
<thead>
<tr>
<th>Unbalanced abnormalities</th>
<th>Balanced abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>−7 or del(7q)</td>
<td>t(11;16)(q23;p13.3)</td>
</tr>
<tr>
<td>−5 or del(5q)</td>
<td>t(3;21)(q26.2;q22.1)</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>t(1;3)(p36.3;q21.1)</td>
</tr>
<tr>
<td>−13 or del(13q)</td>
<td>t(2;11)(p21;q23)</td>
</tr>
<tr>
<td>del(11q)</td>
<td>inv(3)(q21q26.2)</td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>t(6;9)(p23;q34)</td>
</tr>
<tr>
<td>del(9q)</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td></td>
</tr>
</tbody>
</table>

Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.

Other Causes of Low Blood Counts or Dysplasia

- Medications
- Viral infections
- Autoimmune disorders
- Other blood disorders
  - (e.g. T-LGL, aplastic anemia)
- Vitamin/Nutritional deficiencies
  - B12, folate, copper
  - Zinc excess
- Toxins
  - Arsenic, chemotherapy, etc.
Milestones in MDS Classification and Prognostication

- **FAB**
  - Low grade: RA, RARS
  - High grade: CMML, RAEB, Int-1 risk, Int-2 risk, High risk

- **IPSS**
  - Low risk
  - Int-1 risk
  - Int-2 risk

- **IWG criteria**
  - Risk adapted Treatment goals

- **WHO**
  - Reclassified
    - CMML: MDS/MPN
    - RAEB-t: AML
    - RCMD vsRA
    - RAEB-1, -2

- **FDA approval**
  - Azacitidine
  - Lenalidomide
  - Decitabine

- **WHO revisions**
  - RCUD
  - Isolated del5q
  - Minimal cytogenetic criteria
  - MDS-SLN
  - MDS-RS
  - MDS-MLN
  - MDS Del5q
  - MDS-EB 1,2

- **Prognosis Refinement**
  - IPSS-R
  - Gene mutations

- **Timeline**
  - 1982
  - 1997
  - 2000
  - 2001
  - 2004-2005
  - 2008, 2016
  - 2011-12
French-American-British Classification

• RARS - abnormal accumulation of iron in red cell precursors, favorable subtype
• RAEB - more blasts (5-19%), higher risk
• RAEB-t (RAEB “in transformation”) - 20-30% blasts - very high risk

<table>
<thead>
<tr>
<th>FAB</th>
<th>Blast %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (refractory anemia)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>RARS (refractory anemia with ringed sideroblasts)</td>
<td>&lt;5% &lt;5%</td>
</tr>
<tr>
<td>RAEB (refractory anemia with excess blasts)</td>
<td>5-9% 10-19%</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>20-30%</td>
</tr>
</tbody>
</table>
### FAB vs WHO 2000 Classification

<table>
<thead>
<tr>
<th>FAB</th>
<th>WHO</th>
<th>Dysplasia</th>
<th>Blast %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (refractory anemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>5q- syndrome</td>
<td>erythroid+mega</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>RCMD</td>
<td>RA</td>
<td>erythroid</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MDS-U</td>
<td>RCMD</td>
<td>erythroid+other</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>Non-erythroid</td>
<td>Non-erythroid</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>RARS (refractory anemia with ringed sideroblasts)</td>
<td>RARS</td>
<td>erythroid only</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>RCMD-RS</td>
<td>erythroid+other</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>RAEB (refractory anemia with excess blasts)</td>
<td>RAEB-1</td>
<td>≥1 lineage</td>
<td>5-9%</td>
</tr>
<tr>
<td></td>
<td>RAEB-2</td>
<td>≥1 lineage</td>
<td>10-19%</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>AML</td>
<td>myeloid+other</td>
<td>20-30%</td>
</tr>
</tbody>
</table>

- **WHO 2000/2008**
  - 5q- syndrome - a very favorable risk subtype that responds to Revlimid
  - RCMD - multilineage dysplasia associated with somewhat higher risk
  - RAEB-t – very high risk - 20-30% blasts now just called AML
<table>
<thead>
<tr>
<th>2008 Name</th>
<th>Abbrev.</th>
<th>2016 Name</th>
<th>Abbrev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia</td>
<td>RCUD (includes RA, RN and RT)</td>
<td>MDS with single lineage dysplasia</td>
<td>MDS-SLD</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts</td>
<td>RARS</td>
<td>MDS with ring sideroblasts*</td>
<td>MDS-RS</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>Del(5q)</td>
<td>Unchanged^</td>
<td>Del(5q) MDS</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>MDS with multilineage dysplasia</td>
<td>MDS-MLD</td>
</tr>
<tr>
<td></td>
<td>(with ring sideroblasts)</td>
<td></td>
<td>MDS-RS-MLD</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td>MDS with excess blasts, type 1</td>
<td>MDS-EB-1</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td>MDS with excess blasts, type 2</td>
<td>MDS-EB-2</td>
</tr>
<tr>
<td>MDS, Unclassifiable</td>
<td>MDS-U</td>
<td>unchanged</td>
<td>MDS-U</td>
</tr>
</tbody>
</table>

* >15% ring sideroblasts, or >5% AND presence of an SF3B1 mutation.

^ May include ≤ 2 cytopenias AND 1 additional chromosome abnormality other than -7/7q; with pancytopenia: MDS-U.

**WHO 2016**

- Instead of “refractory anemia,” decided to just call it MDS
- RCMD now called MDS-MLD, RAEB now called MDS-EB
- MDS-U- MDS-SLD or del(5q) MDS with pancytopenia or 1% circulating blasts- similar prognosis to MDS-MLD
Milestones in MDS Classification and Prognostication

- FAB
  - Low grade: RA, RARS
  - High grade: CMML, RAEB

- IPSS
  - Low risk
  - Int-1 risk
  - Int-2 risk
  - High risk

- IWG criteria
  - Risk adapted Treatment goals

- WHO
  - Reclassified
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  - MDS-EB 1,2

- Prognosis Refinement
  - IPSS-R
  - Gene mutations

Timeline:
- 1982
- 1997
- 2000
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- 2004-2005
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- 2011-12
# 1997 International Prognostic Scoring System

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)</td>
<td></td>
<td>&lt; 5%</td>
<td>5%-10%</td>
<td>--</td>
<td>11%-20%</td>
<td>21%-30%</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td></td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td></td>
<td>0 or 1</td>
<td>2 or 3</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* Karyotype class:
  - Good = normal, -Y, del(5q) alone, del(20q) alone;
  - Intermediate = other karyotypes;
  - Poor = chromosome 7 abnormalities or complex;

** Cytopenias: Hb < 10 g/dL, ANC < 1800/uL, platelets < 100,000/uL

## Risk Groups

<table>
<thead>
<tr>
<th>IPSS</th>
<th>Low</th>
<th>Int-1</th>
<th>Int-2</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.5-1.0</td>
<td>1.5-2.0</td>
<td>2.5-3.5</td>
</tr>
</tbody>
</table>
OS and Freedom from AML by IPSS Score

Freedom from AML evolution

Overall Survival

*Estimated survival and risk of AML transformation.

# IPSS-R (2012) - More cytogenetic groups and degree of cytopenias

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes (19 categories)</th>
<th>Median survival (mo)</th>
<th>Proportion of pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>60.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p), der(1;7)</td>
<td>48.6</td>
<td>65.7</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), abnormal 17q, +19, +21, any other single or double abnormality not listed, 2 or more independent clones</td>
<td>26.1</td>
<td>19.2</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3q), -7, double abnormality include -7/del(7q), complex with 3 abnormalities</td>
<td>15.8</td>
<td>5.4</td>
</tr>
<tr>
<td>Very poor</td>
<td>Very complex with &gt;3 abnormalities</td>
<td>5.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

## VARIABLE

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>0 pts</th>
<th>0.5 pts</th>
<th>1 pt</th>
<th>1.5 pts</th>
<th>2 pts</th>
<th>3 pts</th>
<th>4 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>V. Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>V. Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤2</td>
<td>&gt;2-&lt;5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td></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 (2012)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
<td>19 %</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5 - 3</td>
<td>38 %</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 - 4.5</td>
<td>20 %</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 - 6</td>
<td>13 %</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
<td>10 %</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Treatment Approaches Largely Depend on Disease Risk

- **Lower Risk**- Transfusions, Erythropoeitin, Revlimid
  - MDS-SLD, MDS-MLD
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1; IPSS-R V. Low, Low

- **Higher Risk**- Vidaza, Dacogen, Transplant
  - MDS-EB (-1, -2)
    - IPSS Int-2, High; IPSS-R High, V. High
Gene Mutations are found in 80-90% of MDS Cases

Sequencing of 111 genes in 738 MDS Patients

Chromosomal Changes in ~50% of MDS


Papaemmanuil et al, Blood 2013
Identification of mutations shifts the IPSS in MDS

Sequencing of 18 genes in 439 MDS Patients

- Low risk, mutation absent (N=87)
- Low risk, mutation present (N=23), P<0.001
- Intermediate-1 risk (N=185)

IWG-PM MDS sample compilation (n=3562):
MDS survival affected by mutation number

Sequencing of 17 genes in 1996 MDS Patients

ASXL1
CBL
DNMT3
A ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1
SF3B1

Bejar R et al, ASH 2015 Abstract #907
SF3B1 Mutations in MDS

• Present in 20% of cases
• Associated with:
  • fewer cytopenias
  • longer survival
  • MDS-RS subtype

Papaemmanuil et al., NEJM 2011
Do Mutations Really Help With Prognostication?

ROC Curves Measure How Accurate a Test is

Mutation Data Actually Adds Little to “All Standard Variables”

- IPSS - % blasts, number of cytopenias, and chromosomes
- “All Standard Variables” - IPSS + degree of cytopenias, more extensive list of chromosomes, multilineage dysplasia, and demographics
- Why? Many poor-risk mutations are associated with poor-risk disease features, e.g. thrombocytopenia

Papaemmanuil et al, Blood 2013
Why Check Mutations at All?

- It can assist with diagnosis
- Some IPSS low risk cases with high risk mutations may require closer observation
- Some IPSS high risk cases may be so high risk that even transplant may not help
- Certain mutations may be targeted using novel therapies on clinical trials
  - IDH mutations
    - AG-221, AG-120
  - SRSF2/SF3B1/U2AF1/ZRSR2
    - H3B-8800
  - TP53 mutations
    - APR-246

TP53 Mutations Predict for Worse Survival After Transplant

Lindsley et al., NEJM 2018

Inhibition of IDH2 with AG-221
How Does MDS Happen?

- All blood cells come from HSCs
- HSCs are the only long lived cells in the blood system
- HSCs develop mistakes in DNA with age or exposure to toxins
- MDS happens when mistakes in DNA impair the function of HSCs
MDS HSCs are Resistant to Standard Therapies

del 5q Persists in HSCs Despite a Clinical Complete Cytogenetic Remission on Revlimid

Tehranchi et al, NEJM 2010;363:1025
Role for Bone Marrow Transplantation

- Remains the only curative therapy for MDS
- Risk may outweigh the benefit if:
  - disease is low risk
  - patient is frail/very elderly
  - disease is very high risk - transplant may not be effective
MDS and Normal HSCs Exhibit Unique Gene Expression Signatures

HSCs from Seven MDS Patients (pre-treatment or untreated) and Two Age-Matched Controls

MDS Compared with Aged Matched Normal HSCs

Gene Expression Signatures Associated with MDS HSCs

2,606 DEGs with FDR <0.01, FPKM>1
MDS is Heterogeneous

HSCs from Six MDS Patients (pre-treatment or untreated)

union of genes in top 10% of loadings on PC2, PC3, PC4
Discovery of Methods to Eradicate MDS HSCs

**Genes Abnormally Expressed in MDS HSCs**

25 predicted to encode cell surface proteins

**CD99 is Highly Expressed in MDS HSCs**
Discovery of Methods to Eradicate MDS HSCs

**MSK MDS-001 (CD34+ cells)**

IC50 - 8.38 µg/ml

***Isotype***  
**anti-CD99 mAb**

**No Ab**  
CD38: 77.1%  
CD34: 20.7%

3.5 µg/ml  
CD38: 84.8%  
CD34: 13.9%

7 µg/ml  
CD38: 95.7%  
CD34: 4.35%

**MDS HSCs**
Summary and Key Points

• MDS is diagnosed by:
  • Low blood counts
  • Dysplasia in the bone marrow
  • +/- Characteristic chromosome abnormalities

• Prognosis in MDS is determined by:
  • % blast cells in the bone marrow
  • How many cytopenias you have and how severe they are
  • Chromosomal abnormalities and gene mutations

• Therapies for MDS are largely recommended based on disease risk

• Mutations may allow for participation in certain clinical trials

• Cure of MDS requires eradication of HSCs
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