WHAT IS MDS?
Myelodysplastic Syndromes

- A group of blood disorders characterized by
  - Bone marrow malfunction related to decreased production of red cells, white cells and platelets
  - The bone marrow cells don’t look normal under a microscope. They look “Dysplastic”
  - Tendency to progress to acute myelid leukemia (AML)

- Overall incidence 3.7-4.8/100,000
  - ≈ 10,000/yr in United States (true estimates ≈ 37,000-48,000)
  - Median age: 70 yrs; incidence: 34-47/100,000 > 75 yrs

Bone marrow stem cells give rise to various blood cells
**STIMULATORY GROWTH FACTORS**
- Erythropoietin (EPO), GCSF, GMCSF, TPO, IL-3, SCF

**HEMATOPOIESIS**
- Stem Cell
  - Progenitors
  - Red Cells
  - W.B.Cs
  - Platelets

**INHIBITORY CYTOKINES**
- TNF, TGF, IL-6, IL-1, Interferons
How does MDS happen?

- Mutations / Chromosomal changes
- Abnormal Stem cell
- Early Stage
  - Immune Cells
  - Fas
  - Cell Death
- Late Stage
  - Leukemia
  - Rapid growth of cells

- TNF-α
- IFN
- VEGF
- TGF
- Inhibitors

- Healthy Stem cells

- Navas et al, Leuk and Lymph, 2009
MDS occurs with increasing age

- Overall incidence: 4.4 per 100,000

SEER Cancer Statistics Review 1975-2008. Section 30, myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMD), and chronic myelomonocytic leukemia (CMML).
How is MDS Diagnosed?

- Most patients have low blood counts
- Low red blood cells - Anemia - Fatigue
- Low white cells - infections
- Low Platelets - Bleeding, Bruising
- Diagnosis requires
  - Peripheral blood examination
  - Bone marrow aspirate and biopsy
  - Genetic and Cytogenetic studies

Chromosomal changes are seen in MDS

Missing pieces of chromosomes: 5, 7, 20
Mutations in genes are found in MDS

Gene mutations: p53, IDH, TET, ASXL, RAS and others

Tested from blood samples
Paid by insurance

Can predict risk

Mutations can be targeted by drugs: IDH and Flt3
• 2 categories of “dysmyelopoietic syndromes”: RAEB and CMML
• 5 categories of myelodysplastic syndromes: RA, RARS, RAEB, RAEB-1, CMML

- Early history
  - il morbo di Guglielmo (1920s)
  - Refractory anemia (1938)
  - Preleukemia anemia (1949/1953)
  - Idiopathic-acquired sideroblastic anemia (1956)
  - Smoldering acute leukemia (1963)
  - “Preleukemia”

- 1976 FAB Cooperative Group Leukemia Classification
- 1982 FAB Group Myelodysplastic Syndromes Classification
- 2008 4th WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues
- 1999 (draft)/2001 (final) 3rd WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues

- ~11 MDS categories
  Changes from 2001 WHO system
  Added: RN and RT (with RA, comprise RCUD), RAEB1 and -2
  Added: RCMD, RCMD-RS, MDS with del(5q), MDS-U, childhood MDS (including provisional RCC)
  Merged: RCMD with RCMD-RS, t-MDS/t-AML due to any cause
  Refined: MDS-U

- ~10 MDS categories
  Changes from 1982 FAB system:
  Added: RN and RT (with RA, comprise RCUD), RAEB1 and -2
  Added: RCMD, RCMD-RS, MDS with del(5q), MDS-U, childhood MDS (including provisional RCC)
  Merged: RCMD with RCMD-RS, t-MDS/t-AML due to alkylators, t-MDS/t-AML due to topoisomerase II inhibitors
  Divided: RAEB into RAEB1 and -2
  Moved: CMML (to MDS/MPD) Eliminated: RAEB-t

# French American British (FAB) Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Blasts in BM</th>
<th>Blasts in Blood</th>
<th>Sideroblasts in BM</th>
<th>Monocytes in Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>&lt; 5%</td>
<td>&lt; 1%</td>
<td>- (&lt; 15%)</td>
<td>&lt; 1 x 10⁹/L</td>
</tr>
<tr>
<td>RARS</td>
<td>&lt; 5%</td>
<td>&lt; 1%</td>
<td>+ (&gt; 15%)</td>
<td>&lt; 1 x 10⁹/L</td>
</tr>
<tr>
<td>RAEB</td>
<td>5% to 20%</td>
<td>&lt; 5%</td>
<td>+/-</td>
<td>&lt; 1 x 10⁹/L</td>
</tr>
<tr>
<td>CMML</td>
<td>5% to 20%</td>
<td>&lt; 5%</td>
<td>-</td>
<td>&gt; 1 x 10⁹/L</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>21% to 29%</td>
<td>&lt; 5%</td>
<td>+/-</td>
<td>&lt; 1 x 10⁹/L</td>
</tr>
<tr>
<td>AML</td>
<td>≥ 30%</td>
<td>&gt; 5%</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

Blast Cells are leukemia cells. The percentage of blast cells is higher in higher risk forms of MDS.

More than 20% Blasts = Leukemia

MDS: Survival Based on FAB Classification

- RARS (n = 125)
- RA (n = 294)
- CMML (n = 126)
- RAEB (n = 208)
- RAEB-T (n = 61)

## Prognosis by WHO Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, n (%)</th>
<th>Transformation to AML, %</th>
<th>Median Survival, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>107 (8.5)</td>
<td>7.5</td>
<td>69</td>
</tr>
<tr>
<td>RARS</td>
<td>138 (11.0)</td>
<td>1.4</td>
<td>69</td>
</tr>
<tr>
<td>RCMD</td>
<td>306 (24.0)</td>
<td>10.0</td>
<td>33</td>
</tr>
<tr>
<td>RCMD-RS</td>
<td>183 (15.0)</td>
<td>13.0</td>
<td>32</td>
</tr>
<tr>
<td>RAEB-I</td>
<td>256 (21.0)</td>
<td>21.0</td>
<td>18</td>
</tr>
<tr>
<td>RAEB-II</td>
<td>235 (18.5)</td>
<td>34.5</td>
<td>10</td>
</tr>
<tr>
<td>MDS 5q-</td>
<td>28 (2.2)</td>
<td>8.0</td>
<td>116</td>
</tr>
</tbody>
</table>

### IPSS Is Most Common Tool for Risk Assessment of MDS

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow blasts</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Chromosomes*</td>
<td>Good</td>
</tr>
<tr>
<td>No. of Cytopenias†</td>
<td>0/1</td>
</tr>
</tbody>
</table>

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1800/µL; platelets < 100,000/µL.

<table>
<thead>
<tr>
<th>Total Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>≥ 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Low</td>
<td>Intermediate I</td>
<td>Intermediate II</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival, yrs</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cytogenetic Abnormalities: IPSS Prognosis

<table>
<thead>
<tr>
<th>Cytogenetic Abnormality</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Y</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Iso del(5q)</td>
<td>48 (6)</td>
</tr>
<tr>
<td>Normal</td>
<td>489 (60)</td>
</tr>
<tr>
<td>Del(20q)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Misc single</td>
<td>74 (9)</td>
</tr>
<tr>
<td>+8</td>
<td>38 (5)</td>
</tr>
<tr>
<td>Double</td>
<td>29 (3)</td>
</tr>
<tr>
<td>Misc double</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Chrom 7 abn</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Misc complex</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Complex</td>
<td>66 (8)</td>
</tr>
</tbody>
</table>

- **Favorable**
- **Intermediate**
- **Unfavorable**

5q- Syndrome: A special type of MDS

- Deletion of chromosome 5
- More Females Affected
- Median age at diagnosis: 68 yrs
- Macrocytic anemia, mild leukopenia, normal or increased platelet count
- Responds to Revlimid
- Indolent course, favorable prognosis
  - AML transformation: 12% to 16%
  - Median survival: > 5 yrs

Faces of MDS
Questions?

Thank You!
Gene Point Mutations - Independent Predictors of OS

Table 2. Hazard Ratios for Death in a Multivariable Model

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 55 yrs or older vs younger than 55 yrs</td>
<td>1.81 (1.20-2.73)</td>
<td>.004</td>
</tr>
<tr>
<td>IPSS risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate 1 vs low</td>
<td>2.29 (1.69-3.11)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Intermediate 2 vs low</td>
<td>3.45 (2.42-4.91)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>High vs. low</td>
<td>5.85 (3.63-9.40)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Mutational status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation present vs absent</td>
<td>2.48 (1.60-3.84)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EZH2 mutation present vs absent</td>
<td>2.13 (1.36-3.33)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ETV6 mutation present vs absent</td>
<td>2.04 (1.08-3.86)</td>
<td>.03</td>
</tr>
<tr>
<td>RUNX1 mutation present vs absent</td>
<td>1.47 (1.01-2.15)</td>
<td>.047</td>
</tr>
<tr>
<td>ASXL1 mutation present vs absent</td>
<td>1.38 (1.00-1.89)</td>
<td>.049</td>
</tr>
</tbody>
</table>
Cytologic Dysplasia: Bone Marrow DysErythropoiesis

 Courtesy of Dr. Bennett and Dr List.
Cytologic Dysplasia: Marrow and Blood DysGranulopoiesis
Cytologic Dysplasia: Marrow and Blood DysMegakaryopoiesis

 Courtesy of Dr. Bennett and Dr List.