Four defining features of MDS

1) Marrow failure / ineffective hematopoiesis (cytopenias)
2) Clonal hematopoiesis (abnormal karyotype, somatic mutations)
3) Characteristic “dysplastic” hematopoietic cell characteristic morphology
4) Instability / tendency to progress to acute myeloid leukemia
Age-dependent nature of MDS (US)

- Overall incidence in this analysis: 3.4 per 100,000
- SEER registry: ~13,000 new US cases per year
- Claims-based data: >40,000 US cases per year


Risk factors for development of MDS

Environmental
- AGING
- Exposure to DNA alkylating agents (chlorambucil, melphalan, cyclophosphamide)
- Exposure to topoisomerase II inhibitors (etoposide, anthracyclines)
- Exposure to ionizing radiation
- Environmental / occupational exposures (hydrocarbons etc.)

Inborn
- Fanconi anemia
- Familial Platelet Disorder with AML Predisposition (*FDS-AML*) (RUNX1, GATA2 mutant)
- Monocytic syndrome: monocytopenia, B/NK lymphopenia, atypical mycobacteria and viral and other infections, pulmonary proteinosis, neoplasms)
- Other congenital marrow failure syndromes or DNA repair defects (Bloom syndrome, ataxia-telangiectasia, etc.)
- Familial syndromes of unknown origin

How Are MDS Diagnosed?

Required to diagnose MDS

A) Low blood counts
   - Especially anemia with high red cell size (MCV)
   - No other cause
B) Increased blasts (≥25% but <20%) or chromosome abnormality (or both)
C) If not B, then lots of dysplasia (cell shape abnormality)
What is “dysplasia”? Rogues’ Gallery #1

- Erythroid
- Myeloid
- Megakaryocytic

- Megoblastoid (open chromosome) maturation
- Multinucleated precursors
- Nuclear budding / karyorrhexis
- Ring sideroblasts

Images: DPS and Elizabeth A Morgan

How is a chromosome analysis (karyotype) done?

- Cells taken from patient
- Cells grown in culture
- Cells harvested and broken apart (lysed)
- Cell debris fixed on a slide
- Chromosomes stained
- Chromosomes counted / band pattern analyzed
- Karyotype assembled and reported

Additional genetic techniques

- Fluorescent in situ hybridization (FISH)
- Sanger DNA sequencing
- Array-based comparative genomic hybridization (aCGH)
- Next-generation DNA sequencing

MDS Molecular Genetics

- Major milestone: in the past several years, we have determined the full set of mutations that cause MDS
- Current research goals: to determine how to use the genetics to guide clinical care, understand MDS biology, and develop better therapies

Rogues’ Gallery #2: MDS mutation landscape

- Epigenetic regulation
  - EZH2 6%
  - DNMT3A 8%
  - ASXL1 14%

- Impaired differentiation
  - RUNX1 5%
  - TP53 8%

- Pre-mRNA splicing
  - SF3B1 22%

- Other
  - SRSF2 11%
  - USP18 6%

- Prognosis

Stenerson OP. Hematology 2009-2009:645-685
**World Health Organization MDS categories (2008)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbrev.</th>
<th>Key Feature</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>Multilineage dysplasia with &gt;1 cytopenia</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts</td>
<td>RARS</td>
<td>&gt;=15% ring sideroblasts</td>
<td>5</td>
</tr>
<tr>
<td>5q- syndrome</td>
<td>5q-</td>
<td>Isolated 5q31 deletion, anemia, hypolobated megakaryocytes</td>
<td>5</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>Multilineage dysplasia with &gt;1 cytopenia</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td>5-9% blasts</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td>10-19% blasts; ±Auer rods</td>
<td>20</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>MDS-U</td>
<td>Does not fit other categories</td>
<td>10</td>
</tr>
<tr>
<td>Childhood MDS</td>
<td>RCC</td>
<td>Often hypocellular, pancytopenia</td>
<td>Rare</td>
</tr>
</tbody>
</table>


**Natural history of MDS: competing risks**

- **MDS Diagnosis**
  - 50% of patients
  - Death from cytopenias and functional cell defects prior to leukemic transformation (INFECTION, bleeding, anemia-related ischemia)
  - Death with MDS, not directly from MDS
  - Death after progression to AML

Dayani F et al Cancer 2010; 116:2174-9

**The “ABCDEFGHI” of MDS Prognosis**

- **A**ge
- **B**last proportion
- **C**ytogenetics
- **D**egree and number of cytopenias
- **E**volution of disease (kinetics)
- **F**unctional status (performance score, comorbidities)
- **G**enetics (molecular)
- **H**ealth care access
- **I**mmunologic status (e.g. absolute lymphocyte count)

**“Old Familiar”: 1997 International Prognostic Scoring System (IPSS)**
- still used for many clinical trials and for transplant assessment

<table>
<thead>
<tr>
<th>Prognostic Variable</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>&lt;5%</td>
<td>5-10%</td>
<td>11-20%</td>
<td>21-30%**</td>
<td>***</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td>0 or 1</td>
<td>2 or 3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Karyotype risk groups: Good = normal, +Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes
**Qualifying Cytopenias: Hb < 10 g/dL, ANC <1800/μL, platelets <100,000/μL
***20% or more blasts now (WHO) considered AML, but was still MDS (FAB) at the time this system was developed

<table>
<thead>
<tr>
<th>Score sum</th>
<th>IPSS Risk Category</th>
<th>Median survival for over age 60 group (years)</th>
<th>Time until 25% get AML (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>Int-1</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Int-2</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;=2.5</td>
<td>Int-3</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>


**1997 IPSS Risk Stratification**

**IPSS limitations**
- Valid only in adult patients with de novo disease
- Validated only at time of diagnosis for patients treated with supportive care alone
- Limited number of karyotypes (5) included
- Insensitive to the degree of cytopenias
- Missing many key variables

**IPSS-R calculation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Very good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogentic risk group</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>52%</td>
<td>&gt;2 - 5%</td>
<td>5 - 10%</td>
<td>&gt;10%</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥120 g/dL</td>
<td>90 - &lt;100 g/dL</td>
<td>&lt;80 g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>≥0.8 x 10^9/L</td>
<td>&lt;0.8 x 10^9/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥150 x 10^9/L</td>
<td>≤50 - 100 x 10^9/L</td>
<td>&lt;50 x 10^9/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Possible range of summed scores: 0-10


**Cytogenetic (chromosome) classification used in IPSS-R**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes</th>
<th>Median survival, years</th>
<th>25% of patients to AML, years</th>
<th>Proportion of patients in this group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(19q), -Y</td>
<td>5.4</td>
<td>N/R</td>
<td>4%</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(1q) alone or with 1 other anomaly, del(11q)</td>
<td>4.8</td>
<td>9.4</td>
<td>72%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), +17q, +20q, any other single or double aberration not listed</td>
<td>2.7</td>
<td>2.5</td>
<td>13%</td>
</tr>
<tr>
<td>Poor</td>
<td>Abnormal 3q, 7q, double aberration include -7/del(7q), complex with 3 abnormalities</td>
<td>1.5</td>
<td>1.7</td>
<td>4%</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt;3 abnormalities</td>
<td>0.7</td>
<td>0.7</td>
<td>7%</td>
</tr>
</tbody>
</table>


**How can MDS be treated?**

**IPSS-R** (see: http://www.mds-foundation.org/ipss-r-calculator/)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% patients (n=7,012; AML data on 6,485)</th>
<th>Median survival, years</th>
<th>Median survival for pts under 60 years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>2.0-3.0</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.5-4.5</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>5.0-6.0</td>
<td>13%</td>
<td>1.5</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;6.0</td>
<td>10%</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>


**Medications currently commonly used for patients with MDS**

- **Hypomethylating agents / DNA methyltransferase inhibitors / epigenetic drugs**
  - Azacitidine (Vidaza®)
    - Approved May 2004
  - Decitabine (Dacogen®)
    - Approved May 2006

- **Blood cell (hematopoietic) growth factors**
  - Epogen (EpoProst®)
  - Darbepoetin alfa (MenaPro®)

- **Immunomodulatory drug (IMiD)**
  - Lenalidomide (Revlimid®)
    - Approved December 2005
  - Thalidomide (Thalomid®)

- **Platelet growth factors**
  - Eltrombopag (Promacta®)
  - Romiplostim (Nplate®)

- **Iron chelators**
  - Deferasirox (Exjade®)
    - Approved November 2005
  - Deferasirox (Decferal®)
    - Approved 1998

- **Red cell growth factors**
  - Pegfilgrastim (Neulasta®)

- **Thalidomide, androgens, other biologics**
  - Thalidomide, androgens, other biologics

- **Immunosuppressive drugs (ATG, CSA)**

- **Chemotherapy or stem cell transplant**

**Only valid for:**
- Adults
- De novo disease
- Treated with supportive care
- At the time of diagnosis

**An approach to MDS**

**Supportive care for all (transfusions and antimicrobials PPN, iron chelation)**

<table>
<thead>
<tr>
<th>Lower-risk MDS (assessed using IPSS-R, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenias(s)</td>
</tr>
<tr>
<td>Anemia only</td>
</tr>
<tr>
<td>No del(5q), EPO &lt;500</td>
</tr>
<tr>
<td>Neutropenia or thrombocytopenia or both</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Higher-risk MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic SCT candidate?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

*Partly based on 2013 NCCN guidelines; see www.nccn.org.*

---

**Romiplostim efficacy in MDS with low platelets**

**Dose:** 750 mg SC or IV weekly (n=568) vs placebo (n=482) x 58 weeks

**IPSS Low/Int-1 with mean platelet count ≤100 x 10^9/L, with bleeding history, or ≤20 x 10^9/L**

**17% complete response rate (8 weeks) >50 x 10^9/L; 8% major response (>30 increment) Most common AEs: fatigue and headache**

<table>
<thead>
<tr>
<th>RBC CR&lt;100K</th>
<th>Disease Relevant Endpoints</th>
<th>Results in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-50</td>
<td>Platelet transfusions not routine:</td>
<td>Bleeding Reduction</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Patients transfused commonly:</td>
<td>Platelet Transfusion Reduction</td>
</tr>
<tr>
<td>≤10</td>
<td>Worst group:</td>
<td>Platelet Count Improvement</td>
</tr>
</tbody>
</table>

**CSRE = clinically significant bleeding events, PTE = protocol-defined PTx events**

<table>
<thead>
<tr>
<th>Romiplostim</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study-defined AML</td>
<td>15 (8.8%)</td>
<td>7 (8.5%)</td>
</tr>
</tbody>
</table>

Kantarjian H et al ASH 2012 abstract

---

**Lenalidomide clinical trials in MDS**

**Del(5q)**

**MDX-001**

N=43, Phase I/II initiated Feb 2002

List A et al NEJM 2005

**MDX-002**

N=214, Phase II initiated July 2003

Raza A et al Blood 2008

67% transfusion independence

Median duration of response >2 years

45% complete cytogenetic remission

**Non-del(5q)**

**MDX-003**

N=148, Phase II initiated July 2003

List A et al NEJM 2006

67% transfusion independence

Median duration of response >2 years

45% complete cytogenetic remission

**MDX-004**

N=205, Phase III initiated July 2005

Finished accrual June 2008

No differences in deep reductions w/ 5 vs 10 mg

Pcytogenetic CR with 10 mg 21/28 d vs 5 mg/d

---

**Who is likely to respond to Erythropoiesis Stimulating Agents (ESAs) in MDS?**

<table>
<thead>
<tr>
<th>Total Score (from below)</th>
<th>IWG 2000 erythroid response rate (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood of response: &gt; +1</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td>Intermediate likelihood: -1 to +1</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td>Low likelihood of response: &lt; -1</td>
<td>7% (n=39)</td>
</tr>
</tbody>
</table>

**Serum EPO level (U/L) | RBC transfusion requirement |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>= +2 pts</td>
</tr>
<tr>
<td>100-500</td>
<td>+1 pt</td>
</tr>
<tr>
<td>&gt;500</td>
<td>= -3 pts</td>
</tr>
</tbody>
</table>

International Working Group (IWG) 2000 Erythroid Response Criteria: >1.5 g/dL Hb increment, or transfusion independence

---

**Suppression of hematopoiesis by an expanded cytotoxic T lymphocyte clone**

**Anti-T cell therapies**

- Anti-thymocyte globulin (ATG)
- Cyclosporin A
- Tacrolimus
- Alemtuzumab
- Others

**Lennox D, Houdek K. Chapter 11: MDS Pathobiology and Clinical Management. 2008**

---

**AZA-001 Survival Study (Higher risk MDS): Azacitidine vs “Conventional Care”**

Log-Rank p=0.0001

HR = 0.58 [95% CI: 0.43, 0.77]

Deaths: AzA = 82, Control = 113

Difference: 9.4 months

Control arm (BSC, 3&7, LDAC)

**Probably better to give 7 days than <7 days IV Ganc at 5C.**

Decitabine (D-0007) registration study outcomes

Outcome Comments
- Improved survival (higher-risk pts) 9.4 months w/ azacitidine [AZA-001]
- Delayed progression to AML 4-6 months [CORT 06011, D-0007, AZA-001]
- Low complete response rate 10-15% [EORTC 06011, D-0007, AZA-001]
- Moderate hematological response rate ~30-60%
- Improved patient-reported outcomes / HRQOL
- Formally studied in CALGB 9221
- Variable duration of response Median for CR: 11-17 months; less for other
- Low early treatment-related mortality Varies by study population, but usually <10%
- Poor survival after HMA failure <6 months


Allogeneic stem cell transplantation for MDS

<10% of patients with MDS currently undergo allogeneic SCT

"Only curative therapy"
Patients who go in to RIC allo SCT with <10% blasts appear to have lower relapse
Optimal timing, pre-transplant therapy, conditioning unclear; usually reserved for IPSS Int-2/High (IBMTR Markov analysis)
Role of HMAs peri transplant, e.g. to dissect GVH from GVL?

Cumulative probability of survival among 374 MDS patients at Pavia, Italy, 1992–2002 (Transfusion-associated hazard ratio for death, 1.58; P=0.005)

Correlation between ferritin and poorer outcome in lower-risk MDS – but does chelation change this? Unclear!

"The risk of RBC transfusion dependence In MDS"

The risk of RBC transfusion dependence In MDS

Based on 426 patients evaluated in Pavia, Italy, 2001–2002

No correlation in RAEB

Based on 426 patients evaluated in Pavia, Italy

MATTEO L. LEUKEMIA RESEARCH 3153 (2007) S2–S6