MDS – Who Gets It, Diagnosis, Treatment

The view from 30,000 feet:

Definitions
What MDS looks like in the U.S.
Treatment – lower-risk
**MDS - definition**

• A heterogeneous clonal hematopoietic disorder derived from an abnormal multipotent progenitor cell

• Characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis

**MDS – definition – in English**

• An *abnormal* bone marrow stem cell ("Grandfather or Grandmother" cell, "Adam or Eve" cell) gives rise to other *abnormal* cells

• These *abnormal* cells grow quickly and "crowd out" the *normal* bone marrow cells, which die and fail to make the usual blood components (red blood cells, white blood cells, platelets)

**MDS - History**

• First published reports date back to 1913.
• First literature review (of 143 people with MDS) in 1973
• First classification system in 1976, revised in 1982
MDS in the Bone Marrow (III)

Cytokines

 bestowed cytokines

in cells

Bone Marrow

Blood Stream

Red Blood Cells
White Blood Cells
Platelets

FAB Classification

<table>
<thead>
<tr>
<th>MDS Subtype</th>
<th>Percentage of Peripheral Blasts</th>
<th>Percentage of Bone Marrow Blasts</th>
<th>AML Transform</th>
<th>Median Survival (months)</th>
<th>Percentage of MDS Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>≤ 1</td>
<td>&lt; 5</td>
<td>10-20</td>
<td>30-65</td>
<td>10-40</td>
</tr>
<tr>
<td>RARS</td>
<td>&lt; 1</td>
<td>&lt; 5</td>
<td>10-35</td>
<td>34-83</td>
<td>10-35</td>
</tr>
<tr>
<td>RAEB</td>
<td>&lt; 5</td>
<td>5-20</td>
<td>&gt; 50</td>
<td>8-18</td>
<td>25-30</td>
</tr>
<tr>
<td>RAEBt</td>
<td>&gt; 5</td>
<td>21-29</td>
<td>60-100</td>
<td>4-11</td>
<td>10-30</td>
</tr>
<tr>
<td>CMML</td>
<td>&gt; 5</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
<td>15-32</td>
<td>10-20</td>
</tr>
</tbody>
</table>


2008 World Health Organization (WHO) Classification of Chronic Myeloid Neoplasm:

- Myeloproliferative neoplasms (MPN): Polycythemia vera, Essential thrombocythemia, Myelofibrosis, Chronic myeloid leukemia
- Acute myeloid leukemia (AML)
- Myelodysplastic syndromes (MDS)
- Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Myelodysplastic syndrome (MDS)
- Acute myeloid leukemia with myelodysplasia-related changes (AML-MRC)

5-9% Blasts

10-19% Blasts

>20% Blasts = AML!
International Prognostic Scoring System

Calculation of prognostic score

<table>
<thead>
<tr>
<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>BM Blast %</td>
<td>&lt; 5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-29</td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Estimation of prognosis

<table>
<thead>
<tr>
<th>Overall Score</th>
<th>IPSS Subgroup</th>
<th>Median Survival (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>Intermediate-1</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Intermediate-2</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Criteria: ANC < 1.5, HGB < 10.0, PLT < 100,000

Good Risk: [−Y, del(5q), del(20q), N1]; Intermediate Risk: [8+, other], Poor Risk: [chr. 7 abn, >3 abn]


Lumpers

Splitters
MDS Classification – The Ultimate Simplification

- **Lower Risk** (Low rate of AML transformation)
  - RA, RARS
  - RCUD, RCMD,
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1 (Score 0-1.0)

- **Higher Risk** (High rate of AML transformation)
  - RAEB (-1, -2)
  - IPSS Int-2, High (Score ≥ 1.5)

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Definitions

**What MDS looks like in the U.S.**

Treatment – lower risk

MDS Incidence Rate: U.S. (II)

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Rate</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3.42</td>
<td>7,076</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>3.20</td>
<td>2,546</td>
<td>31.7</td>
</tr>
<tr>
<td>2002</td>
<td>3.28</td>
<td>2,349</td>
<td>33.2</td>
</tr>
<tr>
<td>2003</td>
<td>3.59</td>
<td>2,491</td>
<td>35.1</td>
</tr>
<tr>
<td>2004</td>
<td>3.8</td>
<td>2,720</td>
<td></td>
</tr>
</tbody>
</table>

Average 3-year survival = 45%

MDS Prevalence

- Not yet determined in the U.S.
- In Germany, one study from Dusseldorf reports it to be ~17/100,000 people.
- If we assume this is similar in the U.S., would translate to ~60,000 people.


MDS: Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing Age</td>
<td>++++</td>
</tr>
<tr>
<td>Male Gender</td>
<td>++++</td>
</tr>
<tr>
<td>Chemotherapy Agents/XRT</td>
<td>++++</td>
</tr>
<tr>
<td>Benzene/Solvents</td>
<td>+++</td>
</tr>
<tr>
<td>Smoking</td>
<td>++</td>
</tr>
<tr>
<td>Pesticides/Herbicides/Fertilizers</td>
<td>++</td>
</tr>
<tr>
<td>Ionizing Radiation</td>
<td>+</td>
</tr>
<tr>
<td>Hair Dye</td>
<td>+</td>
</tr>
</tbody>
</table>

Slide Courtesy of S. Strom
How is MDS Diagnosed?

- Many are asymptomatic but have abnormal blood tests
  - Anemia, low platelets, or low white cells
- Those who do have symptoms may complain of:
  - Fatigue
  - Decreased appetite or energy
  - Infections
  - Bleeding

Anyone a stranger to this???

Patient Survey Data: How MDS Was Described

Sekeres et al. Blood 2009;114:
The number of days per month that physical or mental health was not good or restricted activities was higher in these MDS patients compared with the overall US population norms.

### Cross-sectional analysis of 4514 MDS patients in the U.S. in 2005-7

- **Age** (Median): Newly diagnosed 71 years
- **Sex** (Mean): Male (Newly diagnosed) 55%
- **Duration of MDS** (Median): 13-16 months
- **MDS Status**: Primary 88 – 93%
- **Secondary**: Chemotherapy 55 – 80%
- **Cause**: Radiation 6 – 21%

Sekeres et al. J National Cancer Inst 2008;100:1542

### U.S. MDS Characteristics

- **Median Hgb**: 9.1 g/dl (IQ range 8-10)
- **Median Plt**: 100k/mm³ (IQ range 56-151)
- **Median ANC**: 1780/mm³ (IQ range 1070-2800)
- **Circulating Blasts**:
  - 1-5%: 16%
  - >5%: 10%

Sekeres et al. J National Cancer Inst 2008;100:1542
Transfusion Burden of MDS Patients

MDS Epidemiology in the U.S.

<table>
<thead>
<tr>
<th>Race/ethnic group</th>
<th>Roman numeral-diagnosed patient</th>
<th>Roman numeral microscopic evaluation</th>
<th>Roman numeral 1</th>
<th>Roman numeral 2</th>
<th>Roman numeral 3</th>
<th>Roman numeral 4</th>
<th>Roman numeral 5</th>
<th>Roman numeral 6</th>
<th>Roman numeral 7</th>
<th>Roman numeral 8</th>
<th>Roman numeral 9</th>
<th>Roman numeral 10</th>
<th>Roman numeral 11</th>
<th>Roman numeral 12</th>
<th>Roman numeral 13</th>
<th>Roman numeral 14</th>
<th>Roman numeral 15</th>
<th>Roman numeral 16</th>
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<tbody>
<tr>
<td>White</td>
<td>1,140</td>
<td>1,000</td>
<td>100</td>
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<tr>
<td>Nonwhite</td>
<td>900</td>
<td>800</td>
<td>80</td>
<td>80</td>
<td>80</td>
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<td>Hispanic</td>
<td>750</td>
<td>650</td>
<td>65</td>
<td>65</td>
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<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>500</td>
<td>400</td>
<td>40</td>
<td>40</td>
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<td>40</td>
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<tr>
<td>Other</td>
<td>250</td>
<td>200</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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</tbody>
</table>

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Treatment – lower-risk
Therapy in MDS (I)

Squeeze every last ounce of production out of the remaining functional stem cells with Erythropoiesis Stimulating Agents (ESAs) and Growth Factors (GFs)

ESAs/GF in MDS: Who Responds?

Treatment response score

<table>
<thead>
<tr>
<th>Score &gt; +1</th>
<th>Score = +1 to +1</th>
<th>Score = -1 to -1</th>
<th>Score &lt; -1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good response (74%, n=34)</td>
<td>Intermediate response (23%, n=31)</td>
<td>Poor response (7%, n=29)</td>
<td></td>
</tr>
</tbody>
</table>

RA, RARS, RAEB


ESA/GF for Low-risk MDS

Table 2: Response rates

What are ESAs?

- Erythropoietin (Procrit)
  - Often administered weekly
- Darbepoietin (Aranesp)
  - Given weekly, or every 2 or 3 weeks

Therapy in Lower-risk MDS (II)

Block the effects of those nasty cytokines (chemicals that kill normal bone marrow cells)

Clinical Development of Lenalidomide in Low/Int-1-risk MDS: Completed Trials

- MDS-001
  - N = 43
  - Phase III initiated Feb 2002
- MDS-003
  - N = 148
  - Phase II initiated July 2003
- MDS-002
  - N = 214
  - Phase II initiated July 2003

Slide courtesy of A. Raza
Lenalidomide in del (5q) MDS: Transfusion Response

<table>
<thead>
<tr>
<th>Feature</th>
<th>MDS-02/03 (%)</th>
<th>MDS-01/PK (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>149 (93)</td>
<td>19 (79)</td>
<td>168 (79)</td>
</tr>
<tr>
<td>Erythroid response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TI (n = 168)</td>
<td>99 (66)</td>
<td>15 (79)</td>
<td>114 (63)</td>
</tr>
<tr>
<td>Minor (n = 164)</td>
<td>13 (9)</td>
<td>1 (5)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>TI + Minor (n = 128)</td>
<td>112 (73)</td>
<td>16 (84)</td>
<td>128 (76)</td>
</tr>
<tr>
<td>Time to response, weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.6</td>
<td>7.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Range</td>
<td>1-49</td>
<td>2-40</td>
<td>1-49</td>
</tr>
</tbody>
</table>


Del (5q): Duration of Transfusion Response

Data as of 04Dec06 (N=114)

Median duration TI = 2.2 years
Median F/U: 1.3 yr (Min 0.1 – Max 4.4 yr)


MDS-004: Randomized Study Design

Planned enrollment (n = 205)

Double-blind phase**

Responders (at least minor erythroid response at week 16): Continued double-blind treatment for up to 52 weeks, relapse or progression.

Non responders: Discontinued double-blind treatment and entered open-label treatment or withdrew from study.

Week 0 4 8 12 16 52

Patients stratified by IPSS score and cytogenetic complexity prior to randomization.

Bone marrow assessments performed at baseline, 12 wk, and every 24 wk thereafter.
MDS-004: Responses (RBC-TI)

*P < 0.001 vs placebo: Bars represent 95% CI

Fenaux et al. Blood 2009;114:944a

LEN in Lower-risk Non-del (5q)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Daily Dose</th>
<th>21-Day Dose</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response, n (%)</td>
<td>41 (41)</td>
<td>51 (45)</td>
<td>92 (43)</td>
</tr>
<tr>
<td>Transfusion Independence</td>
<td>26 (28)</td>
<td>30 (26)</td>
<td>56 (26)</td>
</tr>
<tr>
<td>Median Hgb change (g/dl)</td>
<td>3.3</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Range</td>
<td>(1.5-9.2)</td>
<td>(1.0-9.6)</td>
<td>(1.0-9.8)</td>
</tr>
</tbody>
</table>

Time to initial response, weeks

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Dose</td>
<td>6.4</td>
<td>4.1-9.0</td>
</tr>
<tr>
<td>21-Day Dose</td>
<td>3.6</td>
<td>2.3-6.4</td>
</tr>
<tr>
<td>All Patients</td>
<td>4.5</td>
<td>2.7-6.7</td>
</tr>
</tbody>
</table>

Responses similar across FAB, IPSS groups

Non-del (5q): Duration of Transfusion Response

Median duration TI: 41 weeks
Range: 8.0–136.4+ weeks
N = 56
Censored
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Treatment – lower-risk
Treatment – Higher-risk – Steve Gore, MD

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