Bone Marrow and MDS Basics

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The Myelodysplastic Syndromes

What we’ll talk about:
• MDS – definition
• Bone marrow basics
• What MDS looks like in the U.S.
• Different MDS subtypes
• Rationale for therapies

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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
The Myelodysplastic Syndromes

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• Bone marrow basics
• MDS in the bone marrow – when the factory doesn’t work
• Different MDS subtypes
• Rationale for therapies

Bone Marrow Basics

Bone Marrow Basics (II)
The Myelodysplastic Syndromes

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- MDS – definition
- Bone marrow basics
- **What MDS looks like in the U.S.**
- Different MDS subtypes
- Rationale for therapies
MDS Incidence Rate: U.S. (I)

• Age-adjusted yearly incidence rate of 3.4 per 100,000

• Translates to approximately 10,000 new cases per year


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>3.29</td>
<td>2,346</td>
<td>31.7</td>
</tr>
<tr>
<td>2002</td>
<td>3.38</td>
<td>2,349</td>
<td>33.2</td>
</tr>
<tr>
<td>2003</td>
<td>3.58</td>
<td>2,481</td>
<td>35.1</td>
</tr>
<tr>
<td>2004</td>
<td>3.8</td>
<td>2,720</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average 3-year survival = 45%


Background Information (I)

• Incidence
  – ~5 per 100,000 people in the general population
  – 22 to 45 per 100,000 in people >70 years
  – Believed to be underestimated due to underdiagnosis

• Number of cases increasing
  – Growing number of older adults
  – More aggressive diagnoses
  – Increased toxic and chemical exposure
  – Not "preleukemia": <1/3 of patients progress to
Risk Factors for Developing MDS (I)

• Age
  – For the incidence rate is 36/100,000 in U.S., 31/100,000 in Dusseldorf, 99/100,000 in England
  – Median age at diagnosis in:
    • U.S. – 71 years
    • China – 49 years
    • Thailand – 56 years
    • Korea – 57 years
    • Japan – 60 years
• Gender
  – 4.5/100,000 for men, 2.7/100,000 for women
• Race
  – In U.S., 3.7/100,000 for Caucasians, 3.3/100,000 for AA, 2.8/100,000 for Asian/pacific Islanders, Hispanics

Risk Factors for Developing MDS (II)

• Congenital
  – Down Syndrome, Shwachman-Diamond, Fanconi’s
  – Familial ?
• Cytotoxic Drugs and Radiation
  – Alkylating agents, topoisomerase inhibitors
  – Lymphoma patients post-transplant
  – Atomic-bomb survivors, XRT for ankylosing spondylitis
  – ? G-CSF/GM-CSF
• Smoking
  – Considered related to non-occupational benzene exposure (RR ~ 1.65)

U.S. MDS Characteristics

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

<table>
<thead>
<tr>
<th>Age (Median)</th>
<th>Newly diagnosed</th>
<th>Established</th>
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<tbody>
<tr>
<td></td>
<td>71 years</td>
<td>72-75 years</td>
</tr>
<tr>
<td>Sex (Mean)</td>
<td>Male (Newly diagnosed)</td>
<td>Female (Established)</td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>51-57%</td>
</tr>
<tr>
<td>Duration of MDS (Median)</td>
<td>13-16 months</td>
<td></td>
</tr>
<tr>
<td>MDS Status</td>
<td>Primary</td>
<td>88 – 93%</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>7 – 12%</td>
</tr>
<tr>
<td>Secondary</td>
<td>Chemotherapy</td>
<td>55 – 80%</td>
</tr>
<tr>
<td>Cause</td>
<td>Radiation</td>
<td>6 – 21%</td>
</tr>
<tr>
<td></td>
<td>Chemical exposure</td>
<td>2 – 5%</td>
</tr>
</tbody>
</table>

Sakeres et al. J National Cancer Inst 2008;100:1542
How Many MDS Patients Require Transfusions?


U.S. Treatment Approaches to MDS

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

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Different MDS Subtypes

**Keep It Simple, Sekeres (KISS) System**

- **Lower-risk**
  - Death of normal cells predominates

- **Higher-risk**
  - Growth of abnormal cells and death of normal cells predominate

MDS Classification – The *Ultimate* Simplification

- **Lower Risk** *(Low rate of AML transformation)*
  - RA, RARS
  - RCMD, RCMD-RS
  - 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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Rationale for Therapies (I)

To review, MDS is complicated because:

• Good cells die too quickly
• Bad cells grow too quickly
• Bad cells make cytokines that make the bone marrow an inhospitable environment for good cells, and that encourage the good cells to die too quickly

Rationale for Therapies (II)

So, to treat MDS, medications should do the following:

• Stimulate good cells to grow
  – Growth factors
• Stop bad cells from growing
  – 5-Azacytidine, decitabine
• Stop the effects of cytokines
  – Lenalidomide

Summary (I)

• MDS is a disorder of the bone marrow that results in inadequate production of red blood cells, white blood cells, and/or platelets.

• MDS can be divided into low-grade and advanced subtypes