Myelodysplastic Syndromes (MDS) Part 1: Diagnosis, Prognosis, Classification, Lower-Risk Treatments

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MDS Definition

- A diverse group of bone marrow failure conditions characterized by 3 key features:
  - Inadequate production of healthy blood cells
    - "Ineffective hematopoiesis"
  - A tendency to progress to acute leukemia (which is defined by ≥20% bone marrow blasts)
  - Abnormal appearing cells under the light microscope... and, in about half of cases, abnormal chromosomes

How Are Patients With MDS Discovered?

- "Incidental finding"
  - Blood count done during evaluation of another condition (not clear early diagnosis helps!)
- Symptoms
  - Fatigue
  - Anemia: shortness of breath, palpitations, pallor, chest pain, leg swelling etc.
  - Neutropenia: infection, mouth sores
  - Thrombocytopenia: easy bruising, bleeding, skin spots ("petechiae")
Key Peripheral Blood Findings

- At diagnosis in MDS:
  - Anemia
    - Hb < 12 g/dL: >90%
    - Hb < 10 g/dL: 54%
  - Neutropenia
    - ANC < 1800 x 10^9/L: 46%
  - Thrombocytopenia
    - Platelets < 100 x 10^9/L: 37%
  - Also: abnormal appearance of red cells, neutrophils, platelets
  - Implies functional defects

Typical MDS Bone Marrow Findings

- Marrow is normocellular or hypercellular (i.e., increased proportion of cells relative to fat)
- About 10% are hypocellular (low cellularity) and can be tough to distinguish from AA
- Cells look abnormal under the microscope ("dysplasia")
  - Wrong number of nuclei
  - Abnormal maturation
  - Missing essential granules
  - May involve red cells, white cells, megakaryocytes (make platelets), or some combination thereof
  - Blasts may be increased
  - Ring sideroblasts might be present (indicate abnormal iron metabolism)

Newest Cytogenetic Prognostic Data in MDS

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Karyotypes (22 groups)</th>
<th>Median survival, months</th>
<th>Time until 25% of patients developed AML, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>5q-, 12p-, 20q-, 11q-, 11q(11q32), normal, any 2 abnormalities including 5q-</td>
<td>51</td>
<td>71.9</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>+4, 3p12q26 abnormalities, 8q, 17q-, 19q-, 21q-, any other single abnormality, any double abnormality not including abnormalities of chromosomes 5q or 7</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>−X, −7 or 7q-, any double abnormality with −7 or 7q, complex with 3 abnormalities</td>
<td>15.6</td>
<td>6</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>Complex with &gt;5 abnormalities</td>
<td>5.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Haase D et al, MDS Foundation Symposium, Patras, Greece 2009
MDS “Mimics”

- Vitamin deficiencies, esp. B12 and folate
- Mineral deficiencies, esp. copper
- Congenital/inborn disorders, e.g. Fanconi anemia
- Infections, e.g. HIV
- Medications, esp. methotrexate, azathioprine, chemotherapeutics
- Hemolytic anemias
- Autoimmune conditions (immune thrombocytopenia, Felty syndrome etc)
- Alcohol abuse
- Other marrow disorders…
  - Aplastic anemia, leukemia, myeloproliferative, large granular lymphocyte disorders

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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 unilineage dysplasia</td>
<td>RA</td>
<td>Anemia and erythroid dysplasia</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>RN</td>
<td>Neutropenia and granulocytic dysplasia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>Thrombocytopenia and megak. dysplasia</td>
<td>&lt;1%</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>S- syndrome</td>
<td>Del(5q)</td>
<td>Isolated 5q deletion, anemia, hypolobated megakaryocytes</td>
<td>5</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RARS-1</td>
<td>Multilineage dysplasia</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>RARS-2</td>
<td>5-9% blasts</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td>10-19% blasts; 2 Auer rods</td>
<td>20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td>Does not fit other categories</td>
<td>10</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>MDS-U</td>
<td>Often hypocellular, panmyelosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Childhood MDS</td>
<td>RCC</td>
<td>Does not fit other categories</td>
<td>10</td>
</tr>
</tbody>
</table>

Natural History of Untreated MDS

The natural history of MDS is highly variable. Some patients have a very guarded prognosis, others live a good quality life for >10 years.

International Prognostic Scoring System (IPSS) - 1997

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

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

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

***20% or more blasts now considered AML, but was still MDS at the time this system was developed


IPSS Risk Categories: Patient Distribution And Outcomes

<table>
<thead>
<tr>
<th>Score sum</th>
<th>IPSS Risk Category</th>
<th>Median survival (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>0.5-1.0</td>
<td>Int-1</td>
<td>3.5</td>
<td>3.3</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>High</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Patient Distribution

IPSS Predicts Overall Survival and AML Evolution In De Novo MDS

Note the variability even within a given IPSS prognostic category.


What Constitutes “Low-Risk MDS”?


<table>
<thead>
<tr>
<th>Adverse risk factor</th>
<th>Assigned score</th>
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<tbody>
<tr>
<td>Karyotype other than normal or isolated 5q</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;=60</td>
<td>2</td>
</tr>
<tr>
<td>Hb &lt;10 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Plt &lt;50 x 10^9/L</td>
<td>2</td>
</tr>
<tr>
<td>Plt 50-200 x 10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>Marrow blasts &gt;=4%</td>
<td>1</td>
</tr>
</tbody>
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A “Rainbow” Of Treatment Options For Lower-Risk Patients With MDS

Observation
Transfusions
Blood Cell Growth Factors
Immunosuppressive Therapy
Immunomodulatory Drugs
Hypomethylating Agents
No clear benefit from early treatment of MDS, unlike “solid tumors”

“Watchful waiting” appropriate for mild blood count abnormalities

Transfusions

- **RBC transfusion**
  - Generally used if Hb < 8 g/dL, but regional variation in practice
  - Some people need Hb kept higher to avoid symptoms
  - Each unit of RBCs has 200-250 mg elemental iron

- **Platelet transfusion**
  - Generally used if platelet count below 10 x 10^9/L, or for bleeding or need for a procedure
  - “Alloimmunization” is a risk – patients stop responding to transfusions

Blood Cell Growth Factors

- **Red cell growth factors**
  - Medicare only pays for those with Hb < 10 g/dL
  - Safety concerns in solid tumors; not yet in MDS

- **White cell growth factors**
  - No survival benefit but may help decrease infx.
  - Sometimes combined with red cell factors

- **Platelet growth factors**
  - Brand new; risks unknown in MDS
  - Reports of increased blasts in a few patients
  - Only approved for immune thrombocytopenia
Immunosuppressive Therapy

Anti-Thymocyte Globulin, ATG (ATGam™)
Made from horse, rabbit, goat
Serum sickness is main issue
Patient selection?

Cyclosporine, CSA (ATGam™)
Widely used to prevent graft rejection in transplant patients

Treatment Options For Lower-Risk Patients

Immunomodulatory Drugs

Lenalidomide (Revlimid™)
Works best in patients with del5q (2/3 respond)
Can cause neutropenia, thrombocytopenia
Effect lasts an average of about 2-3 years
Cost issues

Used mostly for higher-risk patients, but some physicians use in lower-risk setting, especially if patient is transfusion-requiring
Optimal dose/schedule not defined
Can cause low blood counts
Interest in combining these with other drugs
Azacitidine shown to improve survival in higher-risk patients

Azacitidine (Vidaza™)
Decitabine (Dacogen™)

Hypomethylating Agents
Most Patients Will Use Several Of These At Some Point

- Observation
- Transfusions
- Blood Cell Growth Factors
- Immunosuppressive Therapy
- Immunomodulatory Drugs
- Hypomethylating Agents

What Do We Mean by “Quality of Life” (QOL)?

- While QOL is to large extent in the eye of the beholder, it is generally considered to have several domains:
  - Presence and Severity of Symptoms
  - Ability to Function
  - Quality of Interpersonal Interactions
  - Sense of Well-Being
  - Transcendence
  - Physical
  - Social
  - Psychological
  - Emotional
  - Intellectual
  - Spiritual

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<td>Transcendence</td>
<td>Intellectual</td>
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<tr>
<td></td>
<td>Spiritual</td>
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Self Reported Fatigue in 359 MDS Patients
Internet Based Quality of Life Study in 359 MDS Patients

Results
• Most MDS patients have a reduced QOL and a significant symptom burden
• >90% of survey respondents complained of “excessive” fatigue
• QOL worse than published controls for both validated instruments (P<0.0001)

• Does Fatigue Correlate With Anemia?
• Fatigue levels were independent of:
  • Hemoglobin levels
  • Transfusion Dependence
  • Not explained by co-morbidities

QOL Research
• Most treatment trials in MDS focus on the “objective” measures of disease activity, and not QOL.
  – If the disease improves, QOL is assumed to follow
  – This may or may not be true!

Questions

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