Overview

• Introduction to MDS
• Pathophysiology
• Clinical Practice
  - Making the diagnosis
  - Risk stratification
  - Selecting therapy
• Future Directions/Challenges

Myelodysplastic Syndromes

• Shared features:
  – Ineffective differentiation and low blood counts
  – Clonal expansion of abnormal cells
  – Risk of transformation to acute leukemia
• Afflicts 15,000 – 45,000 people annually
• Incidence rises with age (mean age 71)

Low Blood Counts

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

Normal Range

Corrupted Hematopoiesis

Myelodysplastic Syndromes: Current Thinking on the Disease, Diagnosis and Treatment
Rafael Bejar MD, PhD
Aplastic Anemia & MDS International Foundation
Regional Patient and Family Conference
July 20th, 2013
Differentiation
Transformation
Secondary AML
Advanced MDS
Early MDS
Normal

**Etiology of MDS**

- **De novo** (idiopathic, primary)
- Ionizing radiation, DNA alkylating agents (chlorambucil, melphalan, cyclophosphamide, etc.)
- Topoisomerase II inhibitors (etoposide, anthracyclines, etc.)

Median age ~71 years; increased risk with aging
Peaks 5-7 years following exposure
Peaks 1-3 years following exposure

**Risk factors for 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 ("FPD-AML") (RUNX1, CEBPA)
  - GATA2 mutant (MonoMAC syndrome: monocytopenia, B/NK lymphopenia, atypical mycobacteria and viral and other infections, pulmonary proteinosis, neoplasms)
  - Other congenital marrow failure syndrome or DNA repair defects (Bloom syndrome, ataxia-telangiectasia, etc.)

- **Antecedent acquired hematological disorders**
  - Aplastic anemia (15-20%)
  - PNH (5-25%)

- **Familial syndromes of unknown origin**
  - Fanconi anemia

**MDS Incidence Rates 2000-2008**

- US SEER Cancer Registry Data

**Age and Sex in MDS**

- Overall incidence in this analysis: 3.4 per 100,000

**Making the Diagnosis**
Aplastic Anemia

Syndromes (MDS)

Diagnostic Overlap

Myelodysplastic Syndromes

Myelodysplastic Syndromes (MDS)

Minimal Diagnostic Criteria

- Abnormal leukemia (AML)
- 5-19% blasts
- 9%
- Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)

Other causes of cytopenia and morphological changes EXCLUDED:

- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (e.g., methotrexate, astatine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, GOUT, disorders, MPN etc.)

Looking for Answers

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

Bone Marrow Biopsy

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

Normal Range

- B12 level - Normal
- Folate - Normal
- Thyroid - Normal
- No toxic medications
- No alcohol use
- No chronic illness

Bone marrow aspirate showed no abnormal cells. The bone marrow biopsy revealed normal findings.

Minimal Evaluation Needed

Diagnosis of MDS is largely MORPHOLOGIC, so you need is:

- Bone Marrow Aspirate/Biopsy
- Complete Blood Count with white cell differential
- Karyotype (chromosome analysis)

Sometimes useful:

- MDS FISH panel - usually if karyotype fails
- Flow cytometry - aberrant immunophenotype
- Genetic Testing - may become standard eventually

Minimal Diagnostic Criteria

- MDS "decisive" criteria:
  - >10% dysplastic cells in 1 or more lineages, or
  - S-10% blasts, or
  - Abnormal karyotype typical for MDS, or
  - Evidence of clonality (by FISH or another test)

Other causes of cytopenia and morphological changes EXCLUDED:

- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (e.g., methotrexate, astatine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, GOUT, disorders, MPN etc.)
Classification of MDS Subtypes

World Health Organization MDS categories (2008)

- Refractory anemia with ring sideroblasts
  - ≥15% of erythroid precursors are ring sideroblasts
- MDS associated with isolated del(5q)
  - ≤20% blasts
  - Del(5q)
- MDS associated with isolated del(20q)
  - ≥15% of erythroid precursors are ring sideroblasts
- MDS/MPN categories (2008)
  - Refractory neutropenia (RN)
  - Refractory thrombocytopenia (RT)
  - RAEB-1
  - Dysplasia with myeloproliferative features
  - TAEL2
  - CBL
  - JMML

World Health Organization MDS/MPN categories (2008)

- Refractory anemia with excess blasts
  - Type 1
  - ≥15% of erythroid precursors are ring sideroblasts
- MDS associated with isolated del(5q)
  - ≤20% blasts
  - Del(5q)
- MDS/MPN – unclassified ('Overlap Syndrome')
  - ≥15% of erythroid precursors are ring sideroblasts

Gene Mutations in MDS

- JAK2
- RUNX1
- TP53
- NOTCH1/2
- MAML
- ZSWIM4
- UMODL1
- EZH2
- RAS
- RUNX1
- PRPF8
- SETBP1
- SF3B1
- SF3B2

Prognostic Risk Assessment

Observed Frequency in MDS

- TET2
- CBL
- TP53
- SF3B1
- SETBP1
- PRPF8

Point Mutations in MDS

- Tyrosine Kinase Pathway
  - JAK2
  - KIT
  - BRAF

- Transcription Factors
  - SP1
  - SF3B1
  - SETBP1

- Others
  - NOTCH1/2
  - MAML
  - ZSWIM4
  - UMODL1

Copy Number Change

- Rare in MDS
  - Rare - often at sites of point mutations
  - About 50% of cases
  - Most Mutations

- Most common
  - Likely in all cases
  - ~80% of cases have mutations in a known gene

- Observed Frequency in MDS
  - 4q
  - -11q
  - 7q
  - 1q
  - 8p
  - 17p
  - -Y

Observed Frequency in MDS

- 4q
- -11q
- 7q
- 1q
- 8p
- 17p
- -Y

*Observed Frequency in MDS*
MDS Risk Assessment

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Diagnosis:**

Refractory cytopenia with unilineage dysplasia

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WHO Prognostic Scoring System

<table>
<thead>
<tr>
<th>WPSS Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td><strong>WHO Category</strong></td>
<td>RA, RAEB, MDS with &lt;30% RAEB-1</td>
<td>RAEB</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
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<tr>
<td><strong>Karyotype</strong></td>
<td>Normal, MDS(11)</td>
<td>A8 others</td>
<td>A8 anomaly of chromosome 5</td>
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<tr>
<td><strong>Hemoglobin</strong></td>
<td>&lt;8 g/dL, in men, &lt;7 g/dL in women</td>
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<td></td>
<td></td>
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<tr>
<td><strong>WPSS Risk Group</strong></td>
<td>Very Low</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
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<td><strong>Points</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>% of Patients</strong></td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Median Survival (years)</strong></td>
<td>&gt;10</td>
<td>8.9</td>
<td>4.5-5.5</td>
<td>1.8-2.5</td>
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*Median survival values for the WHO were estimated from Malcovati et al. Blood. 2011;117:5430-40.*

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International Prognostic Scoring System

<table>
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<tr>
<th>IPSS-Revised (IPSS-R)</th>
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MDS Risk Assessment

65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Diagnosis:**

Refractory cytopenia with unilineage dysplasia

- WPSS - Very Low Risk
- IPSS - Low Risk
- IPSS-R - Very Low Risk

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Risk Adapted Therapy
**Treatment Options for MDS**

- Observation
- Erythropoiesis stimulating agents
- Granulocyte colony stimulating factor
- Iron chelation
- Red blood cell transfusion
- Platelet transfusion
- Lenalidomide
- Immune Suppression
- Hypomethylating agent
- Stem cell transplantation

**Clinical Trials** – always the best option

**MDS Risk Assessment**

- 65 year-old woman with mild anemia and a platelet count that fell slowly from 230 to 97 over the past 3 years.

**Guidelines for Lower Risk MDS**

**Primary Goal:** to improve QUALITY OF LIFE

1. Do I need to treat at all?
   - No advantage to early aggressive treatment
   - Observation is often the best approach

2. Are transfusions treatment?
   - No! They are a sign that treatment is needed.

**Guidelines for Lower Risk MDS**

**Primary Goal:** to improve QUALITY OF LIFE

- IPSS: Low/Intermediate-1
- WPSS: Very Low, Low, Intermediate

**Guiding Questions**

- If del(5q) is clinically significant and there are other cytogenetic abnormalities:
  - Clinical relevance of cytopenia or neutropenia

- If cytogenetics negative:
  - Supportive care as an adjunct to treatment

**Treating Lower Risk MDS**

**Primary Goal:** to improve QUALITY OF LIFE

What if treatment is needed?

1. Is my most effective therapy likely to work?
   - Lenalidomide (Revlimid)

   In del(5q) – response rates are high
   - 50%-70% respond to treatment
   - Median 2-years transfusion free!

**Treating Lower Risk MDS**

**Primary Goal:** to improve QUALITY OF LIFE

Is my second most effective therapy likely to work?

- Red blood cell growth factors
- Erythropoiesis Stimulating Agents (ESAs)
- Darbepoetin alfa (Aranesp)
- Epoetin alfa (Procrit, Epogen)
- Lance Armstrong Juice
### Erythropoiesis Stimulating Agents

**Primary Goal:** to improve QUALITY OF LIFE

- ESAs
  - TPO mimetics
  - G-CSF (neupogen)

*ESAs – act like our own erythropoietin*

<table>
<thead>
<tr>
<th>Serum EPO level (U/L)</th>
<th>RBC transfusion requirement</th>
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<tbody>
<tr>
<td>&lt;460</td>
<td>+2 pt</td>
</tr>
<tr>
<td>460-500</td>
<td>+1 pt</td>
</tr>
<tr>
<td>&gt;500</td>
<td>-3 pt</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td>3</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td>2</td>
<td>7% (n=10)</td>
</tr>
</tbody>
</table>

**Note:**
- Hypoplastic bone marrow (too few cells)
- EPO <200 and <5% blasts predictive

### Growth Factor Combinations

**Primary Goal:** to improve QUALITY OF LIFE

- ESAs
  - TPO mimetics
  - G-CSF (neupogen)

*ESAs can be combined with G-CSF*
- response rate of 46.6%, EPO <200 and <5% blasts predictive

*ESAs can be combined with Lenalidomide*
- response rate of 31% to Len, 52% to both. Ti 18.4% vs. 32.0%

*ESAs can be combined with Azacitidine – not yet standard*

### Thrombopoietin Mimetics

**Primary Goal:** to improve QUALITY OF LIFE

- ESAs
  - TPO mimetics
  - G-CSF (neupogen)

*Eltrombopag and Romiplostim - approved, but not in MDS*

*Initial concern about increasing blasts and risk of AML*

*Follow-up suggests Romiplostim safe in lower risk patients*

### Treating Lower Risk MDS

**Primary Goal:** to improve QUALITY OF LIFE

*What my next most effective therapy?*
- Immunosuppression

*Some MDS patients have features of aplastic anemia*
- Hypoplastic bone marrow (too few cells)
- PNH clones
- Certain immune receptor types (HLA-DR15)

### Immune Suppression for MDS

**Primary Goal:** to improve QUALITY OF LIFE

*Swiss/German Phase III RCT of ATG + Cyclosporin (88 patients)*

*Mostly men with Lower Risk MDS*

*CR+PR: 29% vs. 9%*

*No effect on survival*

*Predictors of Response:*
- hypoplastic aspirate
- lower aspirate blast %
- younger age
- more recent diagnosis


### Hypomethylating Agents

**Inhibitors of DNA methyl transferases:**

- Both incorporate into DNA and cause hypomethylation (5-aza > azacitidine)

*AZA preferentially causes DNA damage and induces apoptosis*
**Azacitidine**

AZA-001 Phase III: AZA vs. Id-ARA-C vs. supportive care

- OS benefit: + 9.5 mos
- Time to AML: 17.8 vs. 11.5 mos
- Ti: 45% vs. 11%

Azacitidine Response:

- ORR: ~50%
- CR: ~17%
- Median time to response: 3 cycles (81% by cycle 6)

**Decitabine**

Decitabine Phase III Trial vs ADOPT 3-Schedule Trial

- Dosed q8h x 3 days per 28 days
- CR: 17%
- CR+PR: 30%

Decitabine Response:

- ORR: ~50%
- CR: 17%
- CR+PR: 32%

- Best response: 50% at 2 cycles
- Major Toxicity:
  - Neutropenia: 31% (FN 11%)
  - Thrombocytopenia: 18%

**Iron Balance and Transfusions**

Daily intake

1.5 mg (0.04%)

Tightly regulated

Daily losses only

1.5 mg (0.04%)

Not regulated!

Every three units of blood

3-4 grams of iron in the body

**What About Iron Chelation?**

More transfusions and elevated ferritin levels are associated with poor outcomes in MDS patients.

- Are these drivers of prognosis or just reflective of disease?
- Retrospective studies suggest survival advantage!

- small prospective and large population based Medicare studies show survival benefit, INCLUDING hematologic responses (11-19%).

- I consider treatment in lower risk, transfusion dependent patients with long life expectancy after 20+ transfusions.

**How to Chelate Iron**

Three ways are FDA approved:

- Deferoxamine (Desferal) – subcutaneous pump 8-12 hrs/day
- Deferasirox (Exjade) – oral chelator
- Deferiprone (Ferriprox) – oral chelator

- But side effects and adverse events can be significant!
  - Deferasirox – renal, hepatic failure and GI bleeding
  - Deferiprone – agranulocytosis (no neutrophils!)

**Guidelines for Lower Risk MDS**

**Primary Goal:** to improve **QUALITY OF LIFE**

1. Do I need to treat?  - symptomatic cytopenias
2. Is LEN likely to work?  - del(5q) ±
3. Are ESA likely to work?  - Serum EPO < 500
4. Is IST likely to work?  - hypocellular, DR15, PNH
5. Think about iron!  - 20 or more transfusions
6. Consider AZA/DEA
7. Consider HSCT or clinical trial!
Guidelines for Lower Risk MDS

Special Considerations:

- **Transfusion Dependence**
  - Indication for treatment – even with AZA/DEC, consider chelation

- **Del(5q)**
  - High response rate to LEN even if other abnormalities

- **Serum EPO level**
  - Used to predict EPO response, > 500 → unlikely to work

- **Indication for G-CSF**
  - Used to boost EPO, not for primary neutropenia

- **Immunosuppressive Therapy**
  - ≤ 60y, hypocellular marrow, HLA-DR15+, PNH clone

Limitations of the IPSS/IPSS-R

- Less than half of patients have relevant cytogenetic abnormalities
- Heterogeneity remains within each risk category, particularly the lower-risk categories
- Excludes therapy related disease and CMML
- Is only validated at the time of initial diagnosis in untreated patients

The IPSS's do not include molecular abnormalities

Mutant Frequency and Distribution

- **TP53**
- **ETV6**
- **RUNX1**
- **ASXL1**
- **EZH2**
- **NKX3.1**
- Tyrosine Kinase Pathway

Impact of Mutations by IPSS Group

- **IPSS Low**
- **IPSS Int1**
- **IPSS Int2**
- **IPSS High**

Overall Survival

- The adverse prognostic impact of the complex karyotype is entirely driven by its frequent association with mutations of TP53
Tracking the Founder Clone

Clonal Evolution

Clinical Sequencing and Banking

Clinical Information

Targeted Massively Parallel Sequencing

Biorepository

Viable Cells
Tumor DNA/RNA
Germline DNA

Clinical Information

Targeted Massively Parallel Sequencing

Extensive Genotypic Annotation

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