Overview

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

Myelodysplastic Syndromes: Current Thinking on the Disease, Diagnosis and Treatment

Rafael Bejar MD, PhD
Aplastic Anemia & MDS International Foundation
Regional Patient and Family Conference
April 5th, 2014

Overview

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

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.

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)
**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*

- **Overall**: 0.1, 0.7, 2.0, 7.5, 20.9
- **Males**: 0.1, 0.7, 2.0, 7.5, 20.9
- **Females**: 0.1, 0.7, 2.0, 7.5, 20.9

**Etiology of MDS**

- **85%**: "De novo" (idiopathic, primary)
- **10-15%**: Ionizing radiation, DNA alkylating agents (chlorambucil, melphalan, cyclophosphamide, etc.)
- **<5%**: 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**
- **GATA2** mutant
  - (MonoMACsyndrome: 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

**Antecedent acquired hematological disorders**

- Aplastic anemia (15-20%)
- PNH (5-25%)
Corrupted Hematopoiesis

Making the Diagnosis

Diagnostic Overlap
**Myelodysplastic Syndromes**

**NCCN Guidelines® Version 2.2013**
Myelodysplastic Syndromes

**INITIAL EVALUATION**

- **Cytopenia(s), suspect myelodysplasia**
  - [Image of NCCN Guidelines]

**Required:**
- Hb & platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping
- Serum erythropoietin prior to RBC transfusion
- RBC folate, serum B12
- Serum ferritin, iron, total iron-binding capacity (TIBC)
- Documentation of transfusion history
- TSH (thyroid stimulating hormone) to rule out hypothyroidism

**Minimum Evaluation Needed**

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

- Bone Marrow Aspiration/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

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**Minimal Diagnostic Criteria**

**Cytopenia(s):**
- Hb <11 g/dL, or
- ANC <1500/μL, or
- Platelets <100 x 10^9/L

**MDS “decisive” criteria:**
- >10% dysplastic cells in 1 or more lineages, or
- 5-19% blasts, or
- Abnormal karyotype typical for MDS, or
- Evidence of clonality (by FISH or another test)

**Other causes of cytopenias and morphological changes EXCLUDED:**
- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)

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**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.

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

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*Slide borrowed from Dr. David Steensma*
**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.

Too many cells in the bone marrow
No extra 'blasts' seen
Chromosomes are NORMAL

**Classification of MDS Subtypes**

**World Health Organization MDS categories (2008)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Blood Findings</th>
<th>Bone Marrow Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia with excess blasts (RAEB)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Refractory anemia with ring sideroblasts (RARS)</td>
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<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Del(5q)</td>
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<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td></td>
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<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS - unclassified</td>
<td>MDS-U</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**World Health Organization MDS/MPN categories (2008)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Blood Findings</th>
<th>Bone Marrow Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia with ring sideroblasts and thrombocytosis</td>
<td>RARS-T</td>
<td></td>
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<tr>
<td>Chronic myelomonocytic leukemia, type 1</td>
<td>CMML-1</td>
<td></td>
<td></td>
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<tr>
<td>Chronic myelomonocytic leukemia, type 2</td>
<td>CMML-2</td>
<td></td>
<td></td>
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<tr>
<td>Aigial chronic myeloid leukemia</td>
<td>aCML</td>
<td></td>
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<tr>
<td>Juvenile myelomonocytic leukemia</td>
<td>JMML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS/MPN – unclassified ('Overlap Syndrome')</td>
<td>MDS/MPN-U</td>
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<td></td>
</tr>
</tbody>
</table>

Genetic Abnormalities in MDS

<table>
<thead>
<tr>
<th>Translocations / Rearrangements</th>
<th>Uniparental disomy / Microdeletions</th>
<th>Copy Number Change</th>
<th>Point Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare in MDS:</td>
<td>Rare - often at sites of point mutations:</td>
<td>About 50% of cases:</td>
<td>Most common:</td>
</tr>
<tr>
<td>t(6;9)</td>
<td>4q</td>
<td>del(5q)</td>
<td>Likely in all cases</td>
</tr>
<tr>
<td>(17q)</td>
<td>7q</td>
<td>del(7q)</td>
<td>*80% of cases have mutations in a known gene</td>
</tr>
<tr>
<td>(11;7)</td>
<td>11q</td>
<td>del(11q)</td>
<td></td>
</tr>
<tr>
<td>t(3;7)</td>
<td>17p</td>
<td>del(17p)</td>
<td></td>
</tr>
<tr>
<td>inv(3)</td>
<td></td>
<td>del(12p)</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td></td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-y</td>
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</table>

Point Mutations in MDS

Prognostic Risk Assessment

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
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>WHO Category</td>
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<tr>
<td>- RA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- RA plus SF</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- MDS with del(5q) alone</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- MDS with del(5q) alone and another abnormality</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- RA plus SF and another abnormality</td>
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</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- normal, del(5q) or del(20q) or both</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- deleted del(5q) or del(20q) or both</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- other abnormalities or not constitutional for chromosome 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL, &lt; 10 in women, &lt; 11 in men)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- absent, &lt; 9, &lt; 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- present, &lt; 9, &lt; 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- normal, &lt; 9, &lt; 8</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

International Prognostic Scoring System

<table>
<thead>
<tr>
<th>IPSS Risk Group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
<td>20%</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Low</td>
<td>1-2</td>
<td>25%</td>
<td>2-4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2-4</td>
<td>15%</td>
<td>5-8</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
<td>20%</td>
<td>1.8-2.5</td>
</tr>
<tr>
<td>Very High</td>
<td>5-6</td>
<td>5%</td>
<td>0.6-1.7</td>
</tr>
</tbody>
</table>

IPSS-Revised (IPSS-R)

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 - Very Low Risk
IPSS-R - Very Low Risk
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.

Normal Range

Diagnosis:
- Refractory cytopenia with unilineage dysplasia
- WPSS - Very Low Risk
- IPSS - Low Risk
- IPSS-R - Very Low Risk

Treating 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

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 → EPO

Erythropoiesis Stimulating Agents

Primary Goal: to improve QUALITY OF LIFE

ESAs – act like our own erythropoietin

<table>
<thead>
<tr>
<th>Serum EPO level (U/L)</th>
<th>RBC Transfusion requirement</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>≥2 units/month</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td>100-500</td>
<td>≥1 unit/month</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>≤1 unit/month</td>
<td>7% (n=39)</td>
</tr>
</tbody>
</table>

Hellstrom-Lindberg E et al / Br J Haem 2003; 120:1037
Growth Factor Combinations

Primary Goal: to improve QUALITY OF LIFE

- 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

- 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:
  - hypocellular aspirate
  - lower aspirate blast %
  - younger age
  - more recent diagnosis
Hypomethylating Agents

Inhibitors of DNA methyltransferases:

Iron Balance and Transfusions

Daily intake
1.5 mg (0.04%)
Tightly regulated

Every three units of blood

3-4 grams of iron in the body

Not regulated!

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 suspension – once per day
Deferiprone (Ferriprox) – oral pill form – 3x per day

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/DEC
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

Future Directions

- 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
The adverse prognostic impact of the complex karyotype is entirely driven by its frequent association with mutations of TP53.
Clonal Evolution

Clinical Sequencing and Banking

Clinical Information

Targeted Massively Parallel Sequencing

Viable Cells
Tumor DNA/RNA
Germline DNA

Extensive Genotypic Annotation

Biorepository

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Naomi Galili

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Sherry Pierce
Gautam Borghaeur

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