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

Rafael Bejar MD, PhD
Aplastic Anemia & MDS International Foundation
Regional Patient and Family Conference
March 19th, 2016

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

Age and Sex in MDS

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

- Familial or Congenital: <2%
- Topoisomerase II inhibitors: 10.25%
- Ionizing radiation: 85%
- "De novo" (idiopathic, primary)
- DNA alkylating agents: 85%

Familial or Congenital
- Familial or Congenital
- Often early onset and part of a larger syndrome
- Peaks 1-3 or 5-7 years following exposure
- Median age ~71 years, increased risk with aging

Corrupted Hematopoiesis

Making the Diagnosis

Diagnostic Overlap

Myelodysplastic Syndromes
Minimum 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

- 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.)

Diagnostic Overlap

Clonal

Non-Clonal

Myelodysplastic Syndromes (MDS)

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

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.

- Normal Range

- 812 level - Normal
- Folate - Normal
- Thyroid - Normal

- No toxic medications
- No alcohol use
- No chronic illness
Abnormal myeloid colony growth: Dysplastic changes in ≥2 myeloid lineages.

Blood findings:
- ≥10% of cells in ≥2 myeloid lineages dysplastic
- ≥5% blasts

MDS/MPN
- CMML
- aCML
- RARS
- ± uniparental disomy

Refactor cytopenia with ring sideroblasts
- CMML
- RARS
- ≥20% blasts
- ≥15% of erythroid precursors are ring sideroblasts

MDS associated with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS associated with multilineage dysplasia
- Del(5q)
- TET2
- ≥10% blasts
- ≥10% of normal promyelocytes

MDS - unclassified
- MDS-U
- ≥20% blasts
- ≥15% of erythroid precursors are ring sideroblasts

Refactor cytopenia with unilineage dysplasia
- RARS
- ≥20% blasts
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

Unilineage dysplasia
- ≥10% of cells in ≥2 myeloid lineages dysplastic
- ≥5% blasts

MDS associated with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts

MDS with isolated del(5q)
- Anemia
- ≥15% of erythroid precursors are ring sideroblasts
WHO Prognostic Scoring System

<table>
<thead>
<tr>
<th>WPSS Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Category</td>
<td>RAS, RAS/TV, TVS with or w/o chrom 12 (absent)</td>
<td>RASD</td>
<td>RARX-1</td>
<td>RARX-2</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Normal, del(5) or more in bone mar</td>
<td>Normal, del(7q) or del(20q)</td>
<td>Normal, del(5q) or del(20q)</td>
<td>Normal, del(5q) or del(20q)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Absent</td>
<td>Normal, 10 g/dL or more</td>
<td>Absent</td>
<td>Normal, 10 g/dL or more</td>
</tr>
</tbody>
</table>

WPSS Risk Group | Points | % of Patients | Median Survival* (yr) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
<td>20%</td>
<td>1.2</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>20%</td>
<td>0 - 9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>19%</td>
<td>1.5 - 4.5</td>
</tr>
<tr>
<td>High</td>
<td>3 - 4</td>
<td>28%</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Very High</td>
<td>5 - 6</td>
<td>7%</td>
<td>0.5 - 1.5</td>
</tr>
</tbody>
</table>

*Median survival ranges for the WPSS were estimated from Malcovati et al. Haematologica. 2011 Oct;96(10):1433-40.

International Prognostic Scoring System

IPSS-Revised (IPSS-R)

International Prognostic Scoring System

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

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

**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.

**Treating Lower Risk MDS**

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

- **What if treatment is needed?**
  - **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!

- **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 \(\rightarrow\) EPO

**Erythropoiesis Stimulating Agents**

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

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

- **ESAs** – act like our own erythropoietin

**Total Score**

<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;150</td>
<td>2 Units / month = ±2 pts</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td>150-500</td>
<td>2 Units / month = ±3 pts</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>3 Units / month = ±6 pts</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**
- **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


*Toma A et al (ASCO Abstract) J Clin Oncol 31, 2013 (suppl; abstr 7002)*

**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

*Hitterman M et al ASH Abstracts, 2013. Abstract P362*  
*Kantarjian H et al ASH Abstracts, 2013. Abstract 4401*

**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 methyl transferases:

**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
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.


What About Iron Chelation?

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!

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
**Mutation Frequency and Distribution**

- TP53
- SFRB1
- SBSF2
- U2AF1
- DNMT3A
- TET2
- RUNXI
- ASXL1
- EZH2

Tyrosine Kinase Pathway
- ETV6
- IDH1 or IDH2
- NPM1

Karyotype

Impact of Mutations by IPSS Group

- TP53
- RUNXI
- ASXL1
- EZH2

TP53 Mutations and Complex Karyotypes

- TP53 Mutated
- Complex Karyotype

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

**Clinical Sequencing and Banking**

Targeted Massively Parallel Sequencing

Clinical Information

Viable Cells

Tumor DNA/RNA

Germline DNA

Biorepository

Extensive Genotypic Annotation
Acknowledgements

MDS Center of Excellence at UCSD
Elizabeth Broome  Huanyou Wang - Hematopathology
Edward Ball  Peter Curtin - BMT Group
Matthew Wiedawelt  Grace Ku
Carolyn Maloney  Caitlin Castello
Sandford Shattil  John Adamson - Hematology Group
Catriona Jamieson  Michael Choi
Erin Reid  Annette Von Drygalski

Bejar Lab
Albert Perez  Sigrid Kets
Tiffany Tanaka  Brian Reilly
Amaan Abidi  Bennett Caughey
Fiona Gowen-Huang

Our amazing CLINIC and INFUSION CENTER nurses and staff
And most of – our incredible patients and families!