Myelodysplastic Syndrome
A Family-Oriented Approach on Diagnosis and Treatment Options

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Assistant Professor
MDS Patient & Family/Caregiver Forum
March 3, 2018
Quote of the Day

“There are two primary choices in life: to accept conditions as they exist, or accept the responsibility of changing them”

- Dennis Waitley
Overview

• Introduction to MDS
• Pathophysiology
• Diagnosis and Risk Stratification
• Treatment Options
• Future Directions/Challenges
What is MDS? (What Dr. Google says?)

- MDS are a group of blood cancers in which the bone marrow does not produce healthy blood cells.

- Is considered a “bone marrow failure disorder”.

- Risk of transformation to acute leukemia.
Mr. T is a 70 year-old male with worsening anemia and thrombocytopenia over the past 2 years.

Patient words: “I am exhausted”; “I feel dizzy”; “I have bruises in my arms”
Aberrant hematopoiesis

Elias HK, et al. Oncogene 2013, 1-12
MDS Features

• Estimated 15,351 new cases from 2009 to 2013.
• Incidence: 4.9 per 100,000.
• Median age 71  M>F
• Clonal disorder: Multi-lineage hematopoietic progenitor.
• Ineffective hematopoiesis with cytopenias
• Symptoms: Fatigue, infection or bleeding
Pathophysiology of MDS
MDS Pathogenesis

- **Incompletely understood**

- Stepwise acquisition of genetic mutations or after exposure to agents.

  **De novo (80%)**
  - Primary
  - No history of previous cancer/radiation
  - Increased risk with aging

  **Secondary MDS (20%)**
  - Previous chemo/radiation
  - DNA alkylating agents peaks 5-7 years
  - Topoisomerase inhibitors peaks 1-3 years
  - Prognosis is usually poor

Increased risk with aging
Molecular Pathogenesis: The Clone Wars

Harada et al Cancer Sci 2015
Bone marrow niche, Immune response and MDS

Ganan-Gomez et al Leukemia 2015 29,1458-1469
CHIP: PRECURSOR TO HEME NEOPLASMS

Clonal Hematopoiesis of Indetermined Potential

# Spectrum of Hematopoietic Disorders

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ICUS</th>
<th>IDUS</th>
<th>CHIP</th>
<th>CCUS</th>
<th>MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic mutation</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Clonal karyotypic abnormality</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Marrow dysplasia</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**ICUS:** Idiopathic Cytopenia of Unknown Significance  
**IDUS:** Idiopathic Dysplasia of Unknown Significance  
**CHIP:** Clonal Hematopoiesis of Indeterminant Potential  
**CCUS:** Clonal Cytopenia of Unknown Significance  

NCCN MDS Version 2.2018
Genes involved in MDS

Diagnosis
Overlap Syndromes

How do we make the diagnosis?

• Signs and symptoms are unspecific:
  a. Fatigue (Anemia)
  b. Infections (Neutropenia)
  c. Bleeding (Thrombocytopenia)

• Laboratory studies showing isolated cytopenia/bycytopenia/pancytopenia.

• Gold standard: Bone marrow biopsy.
# Diagnostic Evaluation

<table>
<thead>
<tr>
<th>Needed for most patients</th>
<th>Needed for some patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history and physical exam</td>
<td>Copper level</td>
</tr>
<tr>
<td>CBC with differential</td>
<td>HIV</td>
</tr>
<tr>
<td>LDH</td>
<td>HLA typing</td>
</tr>
<tr>
<td>Reticulocyte counts</td>
<td>Flow cytometry</td>
</tr>
<tr>
<td>Blood smear</td>
<td>FISH</td>
</tr>
<tr>
<td>Serum EPO</td>
<td>Molecular testing</td>
</tr>
<tr>
<td>Iron, ferritin, folate and vitamin B12</td>
<td>Check for congenital medical conditions</td>
</tr>
<tr>
<td>Thyroid function</td>
<td></td>
</tr>
<tr>
<td>Bone marrow biopsy and aspiration</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic testing</td>
<td></td>
</tr>
</tbody>
</table>
Bone marrow examination

Bone marrow biopsy

Iliac crest (pelvis)

Aspiration needle insertion site
Diagnostic Confirmation

- Signs and symptoms
- Laboratory studies
- Pathology confirmation:
  - Dysplasia in red cells/white cells and/or platelet precursors
  - Blasts < 20%
  - Clonality demonstrated in chromosomes, FISH or molecular studies.
MDS Case

- Mr. T had the following labs: WBC: 5000, Hb:8, Plts: 30,000
- Bone marrow biopsy: MDS, Cytogenetics: 5q- blasts 3%
# WHO 2016 MDS CLASSIFICATION

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)</td>
<td>Single cytopenia or bicytopenia. No blast</td>
<td>Unilineage dysplasia &lt;5% blasts &lt;15% ringed sideroblasts</td>
</tr>
<tr>
<td>MDS-SLD with ring sideroblasts</td>
<td>Anemia No blasts</td>
<td>Erythorid dysplasia only. &gt;15% ringed sideroblasts &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with multilineage dysplasia -MDS-MLD with ring sideroblasts</td>
<td>Cytopenias &lt;5% blasts No Auer rods &lt;1 x 10^9 monocytes</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td>MDS with isolated del 5q</td>
<td>Anemia No or rare blasts</td>
<td>Increased megakaryocytes with hypolobulated nuclei &lt;5% blasts</td>
</tr>
<tr>
<td>MDS with excess blasts -MDS-EB1 -MDS-EB2</td>
<td>Cytopenias 1: &lt;5% blasts 2: 5-19% blasts</td>
<td>1: 5-9% blasts 2: 10-19% blasts</td>
</tr>
<tr>
<td>MDS unclassifiable (MDS-U)</td>
<td>Cytopenias</td>
<td>Dysplasia in &lt;10% of cells plus CG abnormality, &lt;5% blasts</td>
</tr>
</tbody>
</table>
What is the prognosis of MDS?

(including Mr. T)
The importance of MDS Scoring Systems

- Treatment decisions. (To treat or not to treat)
- Key factors:
  - MDS subtype
  - Percent of blast cells
  - Chromosome changes
<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts (%)</td>
<td>&lt;2%</td>
<td>&gt;2-&lt;5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;10</td>
<td>8-10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt;100,000</td>
<td>50-100,000</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>&gt;0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cytogenetics Risk Grouping**

<table>
<thead>
<tr>
<th>Cytogenetic Types</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 11q, -Y</td>
<td>5.4 y</td>
</tr>
<tr>
<td>Normal, del 5q, del 12p, del 20, del 5</td>
<td>4.8</td>
</tr>
<tr>
<td>Del 7q,+8, +19, i17q, any other single or double independent clones</td>
<td>2.7</td>
</tr>
<tr>
<td>-7, inv(3), t3q, del 3q, double including -7/del 7q, complex: 3 abnormalities</td>
<td>1.5</td>
</tr>
<tr>
<td>Complex&gt; 3 abnormalities</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Score**

<table>
<thead>
<tr>
<th></th>
<th>&lt;1.5 Very Low</th>
<th>&gt;1.5-3 Low</th>
<th>&gt;3-4.5 Intermediate</th>
<th>&gt;4.5-6 High</th>
<th>&gt;6 Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>8.8</td>
<td>5.3 years</td>
<td>3</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Risk of AML in 25% of patients</td>
<td>NR</td>
<td>10.8 years</td>
<td>3.2</td>
<td>1.4</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Survival according to IPSS-r category

AML evolution per IPSS-R category
TREATMENT
MDS Treatment Myths and Facts

• “One size fits all”: Risk-oriented treatment
• “All you need is chemotherapy”: Chemo is only one option among many
• “I am too old to get treatment”: QOL and survival are treatment goals
• “Transplant is not an option”: It is for some patients
Treatment Goals

Very low Low Risk MDS

Int-2 High Risk MDS

GOALS OF CARE

Improve quality of life
Improve transfusion independence
Improve marrow function
Cure!

Decrease risk of leukemic transformation
Improve survival
Improve quality of life
Cure!
Low Risk MDS Treatment

- Observation
- Transfusions
- Iron chelation
- Hematopoietic growth factors
- Immunosuppressive therapy
- Immunomodulatory drugs (Lenalidomide)

This is my favorite one!

Transfusion Independency: Key Goal on MDS

- Transfusion-dependent patients had worse OS than transfusion-independent patients (HR: 2.16; \(P < .001\))

*Excludes isolated del(5q)
Serum Ferritin is Predictive of Survival and Risk of AML in MDS

- Iron overload is a prognostic factor for OS and transformation to AML

Iron Chelation and Survival

Survival is better in all cases!

# Hematopoietic Growth Factors

<table>
<thead>
<tr>
<th></th>
<th>Generic Names</th>
<th>Brand Names</th>
<th>Mechanism of Action</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESA</strong></td>
<td>Epoetin alfa, Darbopoietin</td>
<td>Epogen, Procrit, Aranesp</td>
<td>Increase red cell counts</td>
<td>40% Epo levels below 500</td>
</tr>
<tr>
<td><strong>GCSF</strong></td>
<td>Filgrastim</td>
<td>Neupogen, Zarxio</td>
<td>Increase Neutrophil counts</td>
<td>38% OS: NR</td>
</tr>
<tr>
<td><strong>1. Thrombopoietin</strong>*</td>
<td>Eltrombopag</td>
<td>Promacta</td>
<td>Increase platelets</td>
<td>47% *</td>
</tr>
</tbody>
</table>

* Not FDA approved yet

ESA and GSCF can be used in combination

Lenalidomide

MDS-002/003: Lenalidomide in MDS

- Phase II studies of lenalidomide efficacy and safety
- Shared eligibility requirements include: IPSS low/int-1 MDS; ≥ 2 U RBC/8 Wks; PLT > 50,000/μL; ANC > 500/μL
- Lenalidomide dosing: 10 mg/day QD or for 21 Days/28 Day cycle
- Response assessment after 24 Wks of treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MDS-002&lt;sup&gt;[1]&lt;/sup&gt; Non-del(5q)</th>
<th>MDS-003&lt;sup&gt;[2]&lt;/sup&gt; del(5q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts, N</td>
<td>214</td>
<td>148</td>
</tr>
<tr>
<td>Erythroid Response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ TI</td>
<td>26</td>
<td>67</td>
</tr>
<tr>
<td>▪ TI + minor*</td>
<td>43</td>
<td>76</td>
</tr>
<tr>
<td>Cytogenetic Response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ CCR</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>▪ CCR + PR</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>Median Hb increase, g/dL</td>
<td>3.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Time to response, Wks</td>
<td>4.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Median treatment duration, Wks</td>
<td>41</td>
<td>&gt; 104</td>
</tr>
</tbody>
</table>

*TI + minor: overall hematologic improvement, including TI and pts with ≥ 50% reduction in transfusions.

MDS-004: Lenalidomide in MDS With del(5q)

- Randomized, double-blind, placebo-controlled, phase III trial

**Stratified by IPSS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RBC-TI ≥ 8 weeks†</th>
<th>RBC-TI ≥ 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide 10 mg PO QD</strong></td>
<td>61.0%</td>
<td>56.1%</td>
</tr>
<tr>
<td>Days 1-21, 28 Day Cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 69/41)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lenalidomide 5 mg PO QD</strong></td>
<td>51.1%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Days 1-28, 28-Day Cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 69/47)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong> PO QD</td>
<td>7.8%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Days 1-28, 28-Day Cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 67/51)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Median duration: not reached; median follow-up: 1.55 yrs
- Overall safety consistent with known lenalidomide safety profile

In Summary

• Observation: Isolated cytopenia, no symptoms.

• Low risk MDS with symptoms:
  - Consider growth factors
  - Transfusions/iron chelation
  - Lenalidomide in 5q MDS
  - Clinical Trial
Going back to Mr. T Case...

• He started treatment with lenalidomide.

• No need for transfusions or growth factors.

• Blood counts started to improve.
High Risk MDS Treatment (What comes first?)

• Hypomethylating Agents: Azacytidine, Decitabine.

• Intense chemotherapy.

• Clinical Trials.

• Stem cell transplant.
## Assessment before treatment

<table>
<thead>
<tr>
<th>Assessment before treatment</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic HCT is a good option for you, and a well-matched donor is available</td>
<td>Allogeneic HCT Azacitidine or decitabine followed by HSCT High intensity chemo followed by HSCT</td>
</tr>
<tr>
<td>Allogeneic HCT may be a good option for you, but a well-matched donor is not available</td>
<td>Azacitidine Decitabine Clinical trial</td>
</tr>
<tr>
<td>Allogeneic HCT is not a good option for you, or a well-matched donor is not available</td>
<td>Azacitidine (preferred) Decitabine Clinical trial</td>
</tr>
</tbody>
</table>

NCCN Guidelines for Patients, 2018
Hypomethylating Agents

HMA Mechanism of Action

Normal cell
- Gene
- Decondensed chromatin
- Gene expression

Leukemic cell
- Gene
- Condensed chromatin
- Tumor suppressor gene silencing
- Leukemic phenotype

Treatment with azanucleosides
- Gene
- Reversal of aberrant DNA methylation
- Decondensation of chromatin
- Activation of silenced genes
- Induction of cellular differentiation and/or apoptosis

Nat Rev Clin Onc 2010
Azacitidine/Decitabine

- Administer every 28 days
- At least 4 to 6 cycles
- Side effects: Nausea/vomiting, decreased counts, infections
Allogeneic Stem Cell Transplant

1. **Stem cells removed from donor**
   - Donor
   - Apheresis machine
   - Blood
   - Stem cells

2. **Patient receives treatment to destroy blood-forming cells**
   - Chemotherapy

3. **Patient receives stem cells**

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Survival after HSCT by age

Myelodysplastic / Myeloproliferative Diseases Overall Survival
Bone Marrow and PBSC Transplantation for Adult Patients by Age at Transplant
Unrelated Transplants Facilitated by NMDP/Be The Match
(2005–2014)

Survival (%)

<table>
<thead>
<tr>
<th>MONTHS AFTER TRANSPLANT</th>
<th>Age 18–54 years (n=1350)</th>
<th>Age ≥ 55 years (n=2355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>60</td>
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<td>24</td>
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<td>48</td>
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<td>10</td>
</tr>
<tr>
<td>54</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
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</tbody>
</table>

Log-rank p-value < 0.001

SOURCE: CIBMTR®, the research program of NMDP/Be The Match
HSCT Challenges

• Donor selection: Related/Unrelated/Alternative donors.

• Patient AND FAMILY selection: Fit for transplant/family support.

• Insurance coverage: This is a big deal!

• Risks versus benefits
CLINICAL TRIALS IN MDS: WHY ARE SO IMPORTANT?
CLINICAL TRIALS IN MDS

• Patient *always* comes first

• The goal is research

• Provides “evidence-based” patient care

• Improves quality of care

• Better than standard of care
MDS trials are available in Albuquerque

<table>
<thead>
<tr>
<th>Trial</th>
<th>Title</th>
<th>Who can participate?</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG-ACRIN NHLBI-MDS</td>
<td>A prospective, multi-center cohort supporting research studies in MDS natural history</td>
<td>MDS diagnosis within 6 months. Other cytopenias MDS/MPN</td>
<td>Open active</td>
</tr>
<tr>
<td>MEI-011</td>
<td>A safety and efficacy study of pracinostat and azacitidine in patients with high risk MDS</td>
<td>High risk MDS</td>
<td>Open active</td>
</tr>
<tr>
<td>SWOG 1612</td>
<td>Azacitidine With or Without Nivolumab or Midostaurin, or Decitabine and Cytarabine Alone in Treating Older Patients With Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome</td>
<td>High risk MDS</td>
<td>In review</td>
</tr>
<tr>
<td>ORIEN</td>
<td>Oncology Research Information Exchange Network</td>
<td>Low and high risk MDS</td>
<td>Open active</td>
</tr>
<tr>
<td>INST 1512</td>
<td>INST 1512: A new drug discovery platform using High throughput Flow Cytometry and a PDX tissue repository in AML and MDS</td>
<td>MDS and AML</td>
<td>Open active</td>
</tr>
</tbody>
</table>
Conclusions

• Treatments for MDS are effective
• Risk stratification is important: Low vs. High
• Low risk treatments are different than high risk MDS treatments.
• Quality of life is always a goal.
• More clinical trials are needed to continue improving outcomes.
THANK YOU

UNM Comprehensive Cancer Center
MDS Foundation
Hematology Team UNM
George Atweh, MD
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Ian Rabinowitz, MD
Dulcinea Quintana, D
Elizabeth McGuire, MD
Jan de la Garza, MSN
Shari Fryer, PA
Jessica Lewis, PA
Cheryl Willman, MD

NEW MEXICO CANCER CARE ALLIANCE
Oliver Rixe
Teresa Stewart
Leslie Byatt
Kathy Anderson
April Encee
Ava Bernardini
Daniel Weishampel

To all patients and their caregivers