MDS Foundation’s Educational
Patient-Caregiver Forum

Stanford University Cancer Center
Saturday, October 28, 2017

The MDSs and their Treatments
Peter Greenberg, MD
Molecular Advances in Understanding MDS
Alex Aleshin, MD
Bone Marrow Transplants for MDS Patients
Lori Muffly, MD
Quality-of-Life Session with Open Discussion
Mary L. Thomas, RN, MS, CNS
The MDSs and their Treatments

Peter Greenberg, MD
Professor of Medicine (Hematology)
Stanford University Cancer Institute
Director, Stanford MDS Center, Hematology Division

October 2017
MDS: Questions

• What is MDS?
• What does it mean for my life?
• Is there treatment for it?
• How should I be treated?
• When?
• Why?
Nature of MDS

• Chronic disease
• Heterogeneous disorders
• Symptomatic cytopenia(s)
• Generally elderly patients
• Co-Morbid conditions
• Potential progression to AML
• Multiple potential therapies
• Impact on quality of life
AGE SPECIFIC RATES OF LEUKEMIAS AND MYELODYSPLASTIC SYNDROMES

RATE PER 100,000 POPULATION

AML
ALL
CML
CLL
MDS

AGES

<20 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85+ ALL
Prognostic Features in MDS

• Clinical
  – CBC, marrow blasts, cytogenetics
  – Age, PS, ferritin, LDH, β2M, marrow fibrosis
  – Treatment/Response

• Molecular
  – Specific mutations
  – Number of mutations
# MDS Morphologic Classifications

<table>
<thead>
<tr>
<th>Marrow Blasts</th>
<th>2008 WHO /NCCN</th>
<th>2016 WHO/NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>RARS</td>
<td>MDS-RSSLD</td>
</tr>
<tr>
<td>“</td>
<td>RCUD, MDS-U del(5q)</td>
<td>MDS-SLD MDS-del(5q)</td>
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<tr>
<td>“</td>
<td>RCMD</td>
<td>MDS-MLD</td>
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<tr>
<td>≥5-9%</td>
<td>RAEB-1</td>
<td>MDS-EB1</td>
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<tr>
<td>≥10-19%</td>
<td>RAEB-2</td>
<td>MDS-EB2</td>
</tr>
<tr>
<td>20-30%</td>
<td>AML-MRC/RAEB-T</td>
<td>AML-MRC/RAEB-T</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>AML/AML</td>
<td>AML/AML</td>
</tr>
</tbody>
</table>
IWG-PM/IPSS-R Prognostic Classification

11 Countries: 7012 patients

- Austria
- Brazil
- Czech Rep
- France
- Germany
- Italy
- Japan
- Netherlands
- Scotland
- Spain
- USA
IPSS-R: Prognostic Features for Disease Status
Greenberg et al, IWG-PM, Blood 9/12, n=7012

• Bone marrow blasts: ≤ or >10%
• Cytogenetic groups: 5 groups
• Depth of abnormal blood counts
  – hemoglobin, neutrophils, platelets
• Age
• Other predictors
  – performance status, serum tests (ferritin, LDH)
IPSS-R prognostic risk-based categories: Survival and risk of AML evolution

Greenberg et al, IWG-PM, Blood 9/2012; www.ipss-r.com
MDS: Incidence of Recurrent Mutations
NCCN Practice Guidelines, Version 1.2018

- >20%:  **ASXL1, TET2, SF3B1***
- 10-20%: **RUNX1, DNMT3A, SRSF2**
- 5-10%: **TP53, EZH2, U2AF1, NRAS, ZRSR2**
- <5%: **CBL, ETV6, SETBP1, IDH1/2, JAK2,**...

*Bold = Poor risk*

* = Good risk
FDA Drug Approvals

- Epo 1993; Darbepoetin 2002  
  - for chemotherapy-induced anemias
- GCSF 1996 (‘90 SUH); Peg-GCSF 2002  
  - for infection (‘93 w/ Epo SUH)
- Azacytidine 2004
- Lenalidomide 2005 for (del)5q MDS
- Decitabine 2006  
  - 2010: 5 day outpatient regimen
- Deferasirox 2005/2015; Deferiprone 2011  
  - for iron chelation
- (Romiplostim, Eltrombopag 2017)
APPROACHES FOR TREATMENT OF MDS

• Clinically Relevant Cytopenia(s)
• Age: > <60 years old
• Performance Status: Excellent, Good, Poor
• Prognostic Risk Category: IPSS/IPSS-R
  – Lower risk: Hematologic improvement
  – Higher risk: Alter disease natural history
• Stem Cell Transplant candidate?
  – Risk category, Age, Performance status, Donor

(www.nccn.org)
**ESA Responses in MDS**

*Santini et al, Blood 122: 2286, 2013; n=456, 29% RBC TD*

**ESA Response Score:**

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<tr>
<th></th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Serum epo &gt;200</td>
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<td>1</td>
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<tr>
<td>Serum ferritin &gt;350</td>
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<td></td>
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<tr>
<td>IPSS-R: Very Low</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
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<td></td>
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<td></td>
<td>Int</td>
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<tr>
<td></td>
<td>High</td>
<td>3</td>
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</table>

**Response**

<table>
<thead>
<tr>
<th>Score</th>
<th>85%</th>
<th>80%</th>
<th>64%</th>
<th>40%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS-R: Very Low</td>
<td></td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>85%</td>
<td>68%</td>
<td>48%</td>
<td>31%</td>
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## MDS: Molecular Subgroup Treatments

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Features</th>
<th>Treatment</th>
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<tbody>
<tr>
<td><strong>SF3B1</strong></td>
<td>Good risk, ring sideroblasts</td>
<td>Luspatercept*</td>
</tr>
<tr>
<td>Other splice genes</td>
<td>Categorizes MDS ontogeny</td>
<td>Splice gene modulators* (H3B-8800)</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Poor risk</td>
<td>+/- Decitabine HDACis* p53 modulator PRIMA1/APR-246*</td>
</tr>
<tr>
<td><strong>IDH2</strong></td>
<td>Distinct mutant subgroup, T-LGL association</td>
<td>Enasidenib</td>
</tr>
<tr>
<td>Del(5q)</td>
<td>Mainly good risk</td>
<td>Lenalidomide</td>
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*Clinical trials
Potential Indications for Iron Chelation

- **RBC transfusions:** ≥20-40
- **Symptomatic anemia/Further RBC txn need**
  -- mainly Low, Intermediate-1 IPSS or BMT candidate
- **Evidence of organ dysfunction**
  -- cardiac, hepatic, endocrine
- **Serum ferritin** >2500→1000; ↑Liver iron content
- **Rx:** Deferasirox orally or Deferrioxamine SQ
Future MDS **Molecular Classifications**

- **Diagnostic/Additive to Clinical Features**
  - Specificity vs Non-clonal cytopenias (‘mimics’)/Biomarkers
  - Polymorphisms α disease susceptibility

- **Prognostic/Additive to Clinical Features**
  - Specific mutations & number of abnormalities
  - Predictive of treatment response
  - IWG-PM/Molecular global project

- **Pathogenetic**
  - Driver vs passenger mutations
  - Gene expression, signaling pathways, epigenetic Δ

- **Therapeutic**
  - Identify & target biospecific driver lesions EARLY
Immune Checkpoint Inhibitors’ Sites of Action

Frequency of Splicing Gene Mutations in Myeloid Malignancies

- **MDS**: 20-30% *SF3B1, SRSF2, U2AF1, ZRSR2*
- **MDS with ring sideroblasts**: 70-90% *SF3B1*
- **AML**: 40-60% *SF3B1, SRSF2, U2AF1, ZRSR2*
- **CMML**: 50% *SRSF2*
Stanford MDS Center: Biologically Focused Clinical Trials

- **Lower risk:**  
  *IPSS-R*  
  VL, Low, Int

- **Higher risk:**  
  *IPSS-R*  
  High, Very High

**Central personnel:**  
Savita Kamble  
Mark Santos  
Alex Aleshin, MD

- **Deferasirox** vs Placebo*
- **Luspatercept**  
  *(TGFβ inhibitor)*
- **Splice gene modulator** *(H3)*

- **AzaC & PD-L1 inhibitor**  
  *(atezolizumab)*
- **Splice gene modulator** *(H3)*

*Completed 10/17
MDS Information Resources

- MDS Foundation
- Aplastic Anemia and MDS Foundation
- Leukemia and Lymphoma Society
- National Comprehensive Cancer Network (NCCN)
- Stanford MDS Center
MDS: Directions

• Clinical
  – Re-structure classification & treatment
    • IWG-PM Molecular mutational characterization
    • Biospecifically targeted treatment approaches
    • Timing/type of Stem Cell Transplantation
    • Include QOL in treatment evaluations
• Biologic: Abnormal stem cells/mutations
• Economic
  – Broad-based forums to evaluate cost effectiveness & potentially decrease costs